Treatment of

BREAST TUMORS

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PREFACE

It is hoped that this book will bring together many loose ends regarding the diagnosis and treatment of breast cancer For such a large topic brevity and conciseness which have been major aims, were hard to maintain, yet have been accomplished The practicing physician today is faced with a plethora of information regarding breast cancer He may even feel that despite his most conscientious efforts his program of therapy lacks something, is old fashioned or unnecessary*

The general nature of breast cancer itself tends to enhance this feeling Certainly it is a disease which occupies a keystone position in the hormone dependent group of cancers It also is responsive to irradiation therapy Its method of operative treatment represents a major tenet of cancer surgery In addition to all this newer concepts of hormone physiology radiation therapy and surgical techniques have added to the complexity of treatment

It is the purpose of this book to broaden our knowledge of breast cancer first by presenting a brief classification of breast tumors, and then discussing the diagnosis treatment and complications of both benign and malignant breast tumors in the light of histology and newer concepts of therapy Special sections on radiotherapy results of treatment, the extended radical mastectomy and treatment by hormone alteration follow to complete the picture without omission of the main theme to renew yet reaffirm the practicing physician s basic knowledge and methods.

To my close friends and colleagues, who have added so much to this book by their collaboration, I offer my thanks I wish also to express my gratitude to the members of the Tumor Boards of the Stanford University Hospital, San Francisco California and of the Veterans Administration Hospital and the U.S Naval Hospital, Oakland, California whose constant presentation of cases and discus

* Crile G., Jr Cancer of the Breast The Surgeon s Dilemma, Cleveland Clinic Quarterly 23 179 1956

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Indeed, I would be greatly remiss if I were not to thank Miss Kay Hyde whose painstaking drawings have added inestimable value and interest to this book, my secretary, Mrs Ernestine Stotler, for her cheerful labors in expertly typing and retyping the manuscript, and finally, the publishers, Lea & Febiger, for their help and cooperation

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Chapter 1

INTRODUCTION

WITHOUT resorting to published statistics it is apparent that tumors of the breast occur frequently enough to occupy a significant place in the practicing physician's daily work be he internist surgeon or general practitioner Adding to deep psychological fears any breast lump will cause in the mind of the average woman, current lay educational trends create concern and anxiety Because of this the patient rushes to her doctor expecting not only reassurance but also action on the part of her physician which will restore her to health Unfortunately the perplexities of breast tumors, and especially cancer often preclude a wholly confident approach on the part of the physician. Yet there are procedures and methods which through years of experience have proved generally to be reliable and are recommended as the measures to take

No treatment can begin without a specific diagnosis and since a lump in the breast may be one of many types the primary step is biopsy Although statistically the chances of such a lump in the average middle aged woman, being malignant are less than its being benign, histologic verification must be obtained On the other hand, indiscriminate biopsy of every lump should be avoided. The art and science of physical diagnosis is still to be pursued.

Once diagnosis is established methodology becomes all important as a successful outcome may very well depend on the techniques applied. Following the initial definitive surgery there will be other considerations such as x ray therapy oophorectomy pregnancy and management of the opposite breast, all of which must then be weighed in the light of the circumstances and conditions at hand. In breast cancer there are many factors which influence the ultimate result. One, therefore considers the patient as a whole in addition to the specific organ involved.

During the life cycle or natural history of a patient with breast cancer it may become apparent that despite initial therapy the patient is doomed and the result, from the standpoint of cure a failure Even then there are steps to take which will *increase longevity in* comfort and reduce pain and morbidity This later stage of breast cancer may be called the "physiologically therapeutic," in contradistinction to the initial or early stage which is called the "anatomically therapeutic." Since the overall purpose of the practicing physician is to cure and alleviate, each of these stages is considered of equal importance.

Chapter 2

PATHOLOGIC CLASSIFICATION OF BREAST TUMORS

THE following classification of tumors of the breast includes the great majority encountered in daily practice

- I. Breast Tumors
  - A Benign
    - 1 Encapsulated
      - *a)* Solid
        - 1) Fibroadenoma
        - 2) Periductal fibroma
      - *b)* Cystic (pseudo-encapsulated)
        - 1) Simple cyst—single or multiple
        - 2) Benign papillomatous cyst
    - 2 Non-encapsulated
      - *a)* Intraductal papilloma
      - *b)* Cystadenoma
      - *c)* Granular cell myoblastoma
  - B Malignant
    - 1 Ductal origin
      - *a)* Malignant intraductal papillary carcinoma
      - *b)* Malignant intracystic papillary carcinoma
      - *c)* Carcinoma—ductal type including comedo-carcinoma
        - 1) Malignant extension to nipple—Paget's disease
    - 2 Glandular origin
      - *a)* Lobular carcinoma *in situ*
      - *b)* Carcinoma—scirrhous, papillary, medullary, colloid or mucoid
    - 3 Mesenchymal tumors
      - *a)* Lobular carcinoma *in situ*
        - 1) Benign form
        - 2) Malignant form—sarcoma or carcinoma
      - *b)* Lymphosarcoma
      - *c)* Sarcoma
- II Hypertrophies and related conditions
  - A Focal interstitial fibrosis
    - 1 With glandular hyperplasia
    - 2 With ductal ectasia (comedo-mastitis)
  - B Focal glandular hyperplasia
  - C Gynecomastia
- III Inflammations
  - A Acute
    - 1 Diffuse
    - 2 Focal
  - B Chronic
  - C Fat necrosis
- IV Anomalies

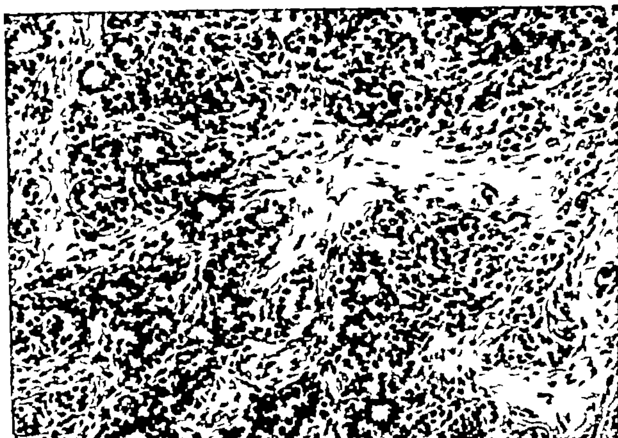


FIG 1 —Sclerosing adenomatosis, florid type Distortion of a hyperplastic lobule by dense scar tissue Approximately 175 ×

The gross appearance of the average carcinoma is distinctive and rarely confused with the focal hypertrophies however it is closely simulated by sclerosing adenomatosis granular cell myoblastoma and chronic fat necrosis Carcinoma has a central grayish white zone of almost cartilaginous hardness when pressed with the tip of a dissecting needle the entire mass is depressed. There are minute grayish white plugs in the mass The edges are poorly defined as a result of the extension of the neoplasm into adjacent breast parenchyma and fat. The ductal carcinomas are limited to ducts which grossly appear ectatic and have minimally thickened walls without gross infiltration of surrounding parenchyma Gross papillary projections and papillomata may be noted in some instances of comedo-mastitis as well as in ductal carcinoma.

Focal interstitial fibrosis with and without glandular hypertrophy and hyperplasia offers the greatest difficulty in the gross differential diagnosis A form of active glandular proliferation combined with fibrosis, commonly called sclerosing adenosis or adenomatosis closely resembles carcinoma in gross appearance (Fig 1) Even after detailed histologic examination it is often difficult to be certain that the lesion is not a carcinoma

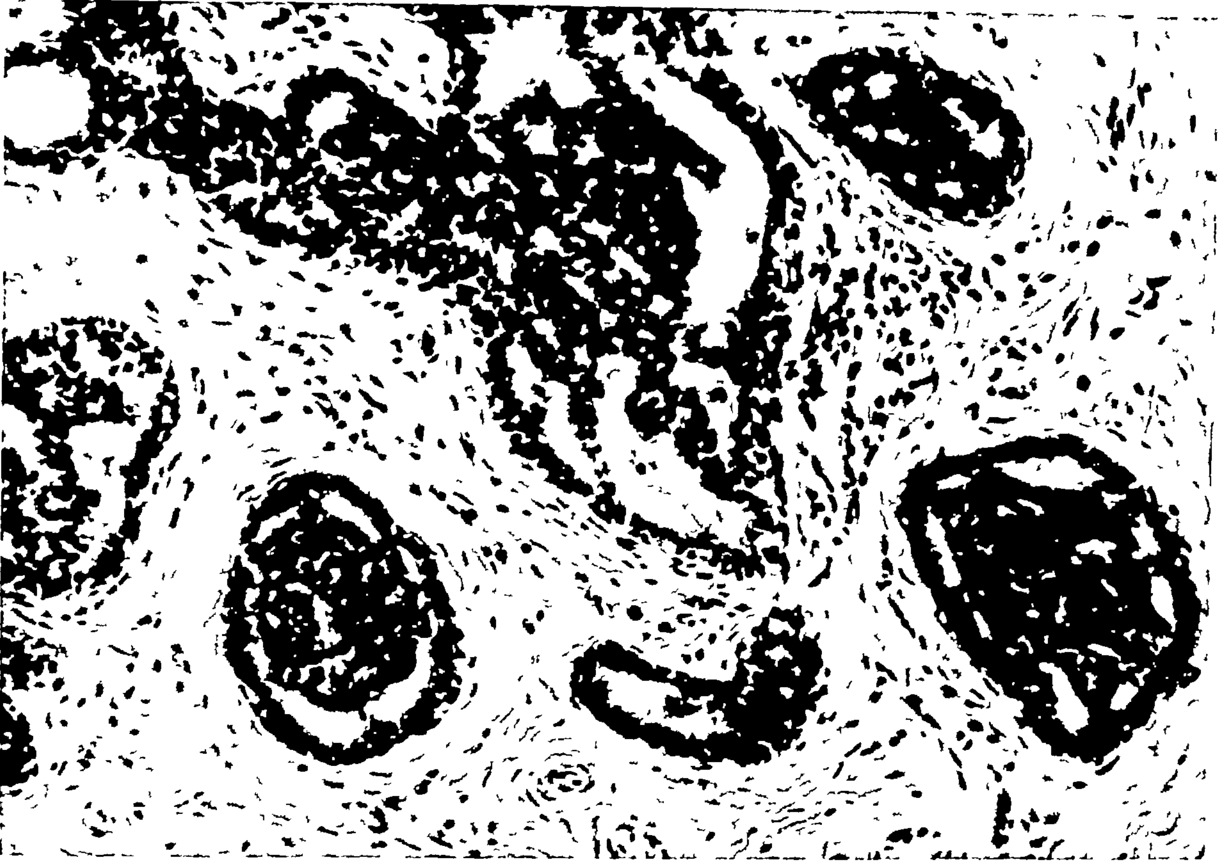


FIG 2—Benign intraductal papillomatosis spreading throughout a group of ducts in a lobule The epithelial cells are small and regular Approximately 175 ×

A variety of lesions are grouped in the hypertrophies The most common of these are so-called blue dome cysts frequently associated with an increase in the amount of fibrous tissue in the adjacent parenchyma Usually, the glands have undergone enlargement and show an increase in the number of cells The ducts are enlarged and lined by several layers of epithelial cells True intraductal papillations are present, and visible grossly The presence of patches of multiple cysts and focal scarring scattered indiscriminately throughout the breast, and often in the opposite breast, does not exclude the possibility that more serious lesions may be present Careful search must be made for small, firm zones of induration in the tissue between the more innocuous cysts

The differentiation of the benign forms of intraductal and intracystic papillary tumors from the malignant depends on the nature of the epithelial cells The benign pattern of uniformity, regularity, lack of cellular atypism and the appearance of secretory function in these cells aids in distinguishing the benign lesions from those malignant forms which are still limited to the duct or cyst (Figs 2 and 3) The pattern of lobular carcinoma *in situ* often does not have many features which permits it to be diagnosed with certainty when compared to a florid form of sclerosing adenomatosis The glandular lobules of carcinoma *in situ* are



FIG 3.—Intraductal carcinoma This metastasizing neoplasm is still limited to a cluster of enlarged ducts The cells fill the ducts in a cribriform arrangement Approximately 175 ×

enlarged and packed with cells which may be uniform in appearance (Fig 4) There is a proliferation of the epithelium of the terminal ductules into the lobules without invasion of the stroma On frozen section examination these non invasive lesions pose a difficult problem and care must be taken not to confuse them with forms of sclerosing adenomatosis, as well as other benign conditions such as hyperplastic apocrine glands

The microscopic pattern of carcinoma of the breast rarely shows a pure form, such as a typical adenocarcinoma. More commonly it is mixed, and includes combinations of scirrhous papillary and medullary patterns, together with some distinctly mucoid or colloid types Grading of these tumors may be difficult in as much as the degree of differentiation will vary according to the pattern in the area under examination The closer the tumor resembles a well-differentiated adenocarcinoma, the easier it is to grade The relatively undifferentiated mixed scirrhous and medullary tumors are usually classified grades III and IV

Carcinoma of the breast gives rise to metastases by way of direct extension infiltration of lymphatics, or through the blood stream There is a greater tendency for lesions in the lateral hemisphere to metastasize to the axillary lymph

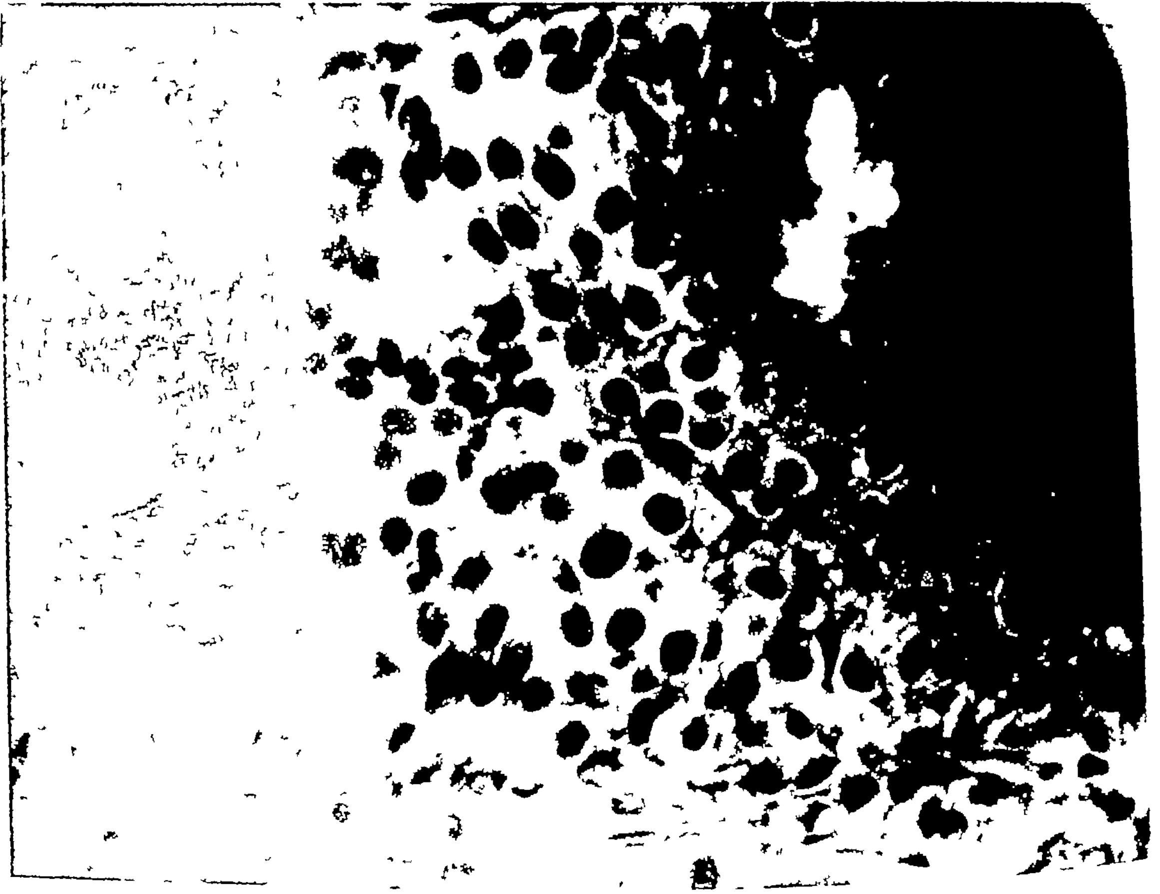


FIG 4 —Lobular carcinoma *in situ* The lobule is greatly enlarged and the usual cells are replaced by packed sheets of polyhedral cells contained by an intact basement membrane Approximately 450 ×

nodes, the medial lesions will more frequently involve the internal mammary chain of nodes The lymphatic extension to the regional lymph nodes is thought to take place as a solid plug of cells in the lymphatics, thus requiring block dissection to avoid cutting through tumor-containing lymphatic pathways Distant metastases involve any organ or system, but there is a predilection for either the skeletal system or the viscera The combination is never excluded Metastases to the endocrine system, particularly adrenals, ovaries, and hypophysis frequently occur. Involvement of the liver by extensive metastases has serious clinical significance in that the impairment of liver function, particularly of hormone metabolism, may affect the tumor by increasing its rate of growth

A breast involved by tumor with concomitant inflammatory change is usually classified as inflammatory carcinoma When both occur simultaneously it is known as the primary type When the inflammatory signs appear in a breast which already contains a carcinoma, it is listed as the secondary type The inflammatory appearance is due to spread of the tumor into the lymphatics of the skin It is more common in the large pendulous breast, and very infrequent

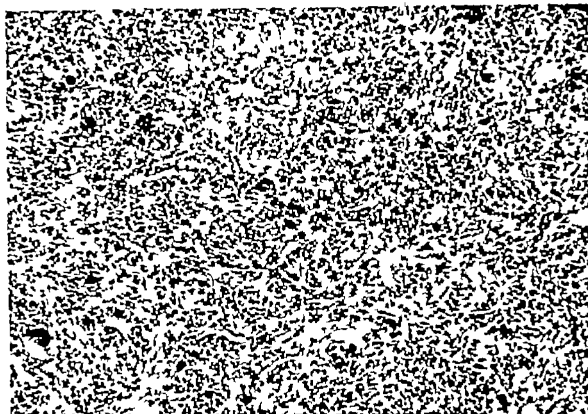


Fig 5 —Sarcomatous appearance of stroma of cystosarcoma phyllodes characterized by multinucleated giant cells and spindle cells Approximately 100 ×

in the senile breast Whenever encountered it signifies an extremely malignant condition with very poor prognosis

The malignant forms of breast tumors are manifold (Fig 5) yet most adhere to a fixed pattern of growth and spread. It is also very difficult to determine prognosis from the microscopic sections alone. For these reasons once diagnosis has been established other criteria relating to the entire picture of the particular tumor in the patient at hand are necessary to determine proper care and treatment These important considerations form the basis of the discussions which follow

Chapter 3

BENIGN TUMORS OF THE BREAST

Few conditions cause as much anxiety and worry to the patient as do tumors of the breast. The reasons are not simple or clear. The breast is, of course, the most superficially placed of all organs where cancer frequently occurs, but there are deep psychogenic reasons which make the thought of loss of the breast terrifying to the average woman.

Five years ago, in our personal practice, we operated on as many cancers of the breast as we did on benign lesions of the breast.[10] For the past three years, our operative records show twice as many benign tumors as cancers. In addition, the number of breast conditions seen and not operated on now almost equals the number in which there was surgical intervention. Similar facts have been reported by McSwain.[7,8] The number of malignant and benign tumors of the breast removed at Vanderbilt University Hospital during the period 1925 through 1945 in comparison with those excised from 1946 through 1949 showed that in the earlier period there were more malignant tumors (352 or 51 per cent) than benign tumors of all types (337 or 49 per cent). In the later period only one-third (114) of the tumors were malignant, two-thirds were benign (231).

The reason for this changed incidence probably is due as much to the efforts of lay education as any supposed change in the nature of the disease itself.[4] Patients are aware of the potential dangers of a breast lump and seek medical advice more readily. This increases the overall number of breast tumors examined, the majority of which are benign. One might say that we are now getting a better cross-sectional index of the general population.

From the physician's point of view a major problem in dealing with tumors of the breast is accuracy in diagnosis. Unfortunately, this usually means tumor removal and microscopic examination which subjects the patient to the physical and mental trauma of surgery. No matter how minor such a procedure may be few operations are attended by more worry and near hysteria. Nevertheless, as Riddell[9] has said, "We must grow more and more accustomed to suspecting malignant disease on less and less clinical evidence." Cancer can only be diagnosed microscopically, and most often presents as a localized lump in the breast similar in many ways to the benign tumors. Since part of the problem of breast cancer is the separation of benign from malignant tumors the importance of the former group is obvious.

CHRONIC CYSTIC MASTITIS

This is a disease of all the mammary tissue but in the majority of instances its clinical picture is localized to a specific area of the breast Most patients will complain of a lump mass or pain in the upper outer quadrant of one breast though the process is undoubtedly bilateral. Clinically one may describe three broad groups of patients with this disease

The first group which may be separated includes young women, usually between eighteen and thirty years of age who complain merely of pain in the breast and on examination exhibit tender firm diffusely thickened areas most commonly found in the upper outer quadrant These have been called painful breasts, mastodynia or mazoplasia all terms which indicate a mild condition. Pain may be fairly intense during the premenstrual phase and is often markedly relieved with the second day of menses A diffuse lumpiness in the premenstrual phase often subsides dramatically with the menstrual flow These patients are often thin, intense emotional women who are greatly worried that the pain may signify cancer In occasional instances the pain may be severe However when reassured that such pain is commonplace in young women, and that the majority of cancers are "painless," most patients require no further therapy Associated gynecologic disorders are seen with this group fibromyomas, menorrhagia or scanty menses, and cervical polyps in addition to thyroid nodules There also will be a history of difficulty in becoming pregnant Hormone therapy is contra indicated, and usually enhances the problem rather than resolves it (*see* p 27) If this condition is due to an abnormal or unbalanced endocrine system caused by excessive estrogen stimulation during the period of maximum ovarian function, certainly the addition of extrinsic hormones serves further to increase this im balance. Whatever the true cause the clinical response to hormone administra tion, androgenic, estrogenic or otherwise has been disappointing [5]

The second and largest group and the one wherein so much confusion exists, is probably a more exaggerated or later form of the mastodynias This condition is called variously Schimmelbusch s disease, benign parenchymatous hyperplasia, adenosis, adenocystic disease and a variety of other names These women often remain childless, are in their late thirties or early forties, premenopausal have irregular menses and are nervous and underweight. They often have small, dense saucer-edged breasts with multiple nodules on palpation Numerous small and large cysts are frequently palpated and on aspiration yield a murky, dark green, thin fluid or a clear straw colored fluid which is not sanguineous. Cytologic studies of the fluid does not show malignant cells Because of a higher and advancing age group these patients require more aggressive treatment, primarily aimed at ruling out cancer The nodularity and thickening are more localized and tumor like Pain and tenderness are not so prominent and changes with the menses not so marked, the process tending to remain constant so that the clinician

finds it difficult to make a diagnosis. Overlying skin dimpling may occur and is seen in about 10 per cent of the patients. This is especially so when breast tissue changes are about the areola margin. If the disease has been of any duration, with noticeable breast changes of engorgement and resolution, axillary lymph nodes become enlarged which further complicates the picture.

The majority of excisional biopsies performed are in this group. Once the diagnosis of cancer has been ruled out routine follow-up examinations at three- to six-month intervals is all that is necessary. Fibrocystic mastitis is probably a self-limiting disease which tends to disappear or resolve after the time of the menopause. Since most of the patients in this group are premenopausal the process may be expected to control itself with time.

The third group are those patients with solitary cysts. This lesion was fully described by Bloodgood[2,3] and the term blue-domed cyst popularized. These patients are older, postmenopausal and frequently show a large amount of fatty infiltration in the breast tissue. The breasts on examination are soft and full without nodularity or thickening. The cyst usually arises suddenly with some associated pain. They usually are discrete, single and tense, occasionally multiple, and unassociated with other systemic or generalized disease. The cysts are filled with thin, turbid, yellow or greenish fluid. Diagnosis of the cyst is not difficult. It exhibits the classical slippery, freely movable characteristic as if the tumor is trying to elude the examining finger. When "cornered" and pressed slightly it feels tense and "gives" a little, eliciting slight or moderate pain. At times it may be very hard, especially if surrounded by a zone of mastitis, and simulate a solid tumor. Rarely is there any skin attachment.

Although aspiration of any breast tumor without obtaining a definitive diagnosis is risky, aspiration of breast cysts is a commonly accepted and approved method of management. On aspiration one may get 5 to 10 cc. of turbid yellow or greenish fluid, often under pressure. Usually, this is all the treatment that is necessary, and after two or three weeks the breast tissue feels smooth and normal at the site of the aspiration. If small localized areas of residual induration persist beyond two or three weeks it is best to perform an excisional biopsy. Aspiration of a simple cyst is a safe procedure provided the patients are carefully selected and both physician and patient are prepared for excision of any residual localized or indurated mass that does not subside after a few weeks. It is not suggested by this that all cysts should be treated first by aspiration, but merely that when the diagnosis is highly suggestive this is one method of treatment which may prevent the necessity of a more major operative procedure in the form of an excisional biopsy.

It should be apparent that not all patients with fibrocystic mastitis can exactly fit into these three broad groups. Many patients will have signs and symptoms which correspond to all three groups, young women may have solitary cysts and older women mastodynia alone.

Grouping all of these patients together, and disregarding their clinical classifi-

cation the patient that is most commonly seen[6] with chronic cystic mastitis will be between forty and forty nine years of age complain of pain in the upper outer quadrant of one breast, and point to a lump which is slightly tender on palpation and which was the cause of her seeking medical advice She will have waited about two to four weeks before consulting her doctor On examination a slightly tender diffuse nodularity will be felt, most marked in the upper outer quadrant. There will be a poorly outlined, thickened, irregular mass which in some patients appears to be composed of multiple small cysts and large, thickened, cord like lobules On palpation these tumefactions will seem to be part of the breast tissue itself and will not move freely Very occasionally there may be skin retraction with slight pulling of the nipple

Because of its somewhat vague nature and because of a still relatively obscure etiology[1] specific treatment is lacking Because chronic cystic mastitis is a disease of all the mammary tissue it is obvious that local excision is not curative Surgery is performed primarily to rule out cancer Statistical evidence which shows an increased (3 to 5 per cent) liability to form cancer in these patients (*see* p 31) is a secondary consideration.

Surgical Technique of Excisional Biopsy

The patient is placed supine on the table with one or both arms extended at right angles on an arm board (Plate 1) The arm board and table mattress are of equal height so that no injury occurs to the arm at the edge of the mattress The arm on the side of the involved breast is held in slight pronation, thumb up so as not to stretch the axillary nerves and musculature It is draped free. The opposite arm is used for intravenous medication and may be draped to the side if desired General anesthesia is used A low ether screen shields the head and neck area from the operative field Fine absorbable sutures are used for all biopsy and other smaller operations on the breast.

In most instances a radial incision in the direction of the duct system is made (Plate 2) Where skin dimpling is present an elliptical incision which encompasses the dimpled area is used (Plate 2) Circumareolar incisions are made for papillomas and sinus tracts as the extent of resection required is less in these cases (Plates 9a and b) Incisions are placed so that they can be completely encompassed by those made for a radical mastectomy should the latter be necessary The use of frozen section analysis and immediate radical operation is done routinely All patients are prepared for this by frank discussion preoperatively

The deeper tissues are incised, and small flaps developed by undermining on each side (Plate 3) By grasping the area with a towel clip in the region of the tumor a large block of tissue is pulled upward and dissected free (Plate 4) This is an optional maneuver Because there is some chance of piercing the tumor with the prongs of the clip thereby spreading malignant cells, dissection of a generous block of tissue surrounding the tumor can be performed without

PLATE 1

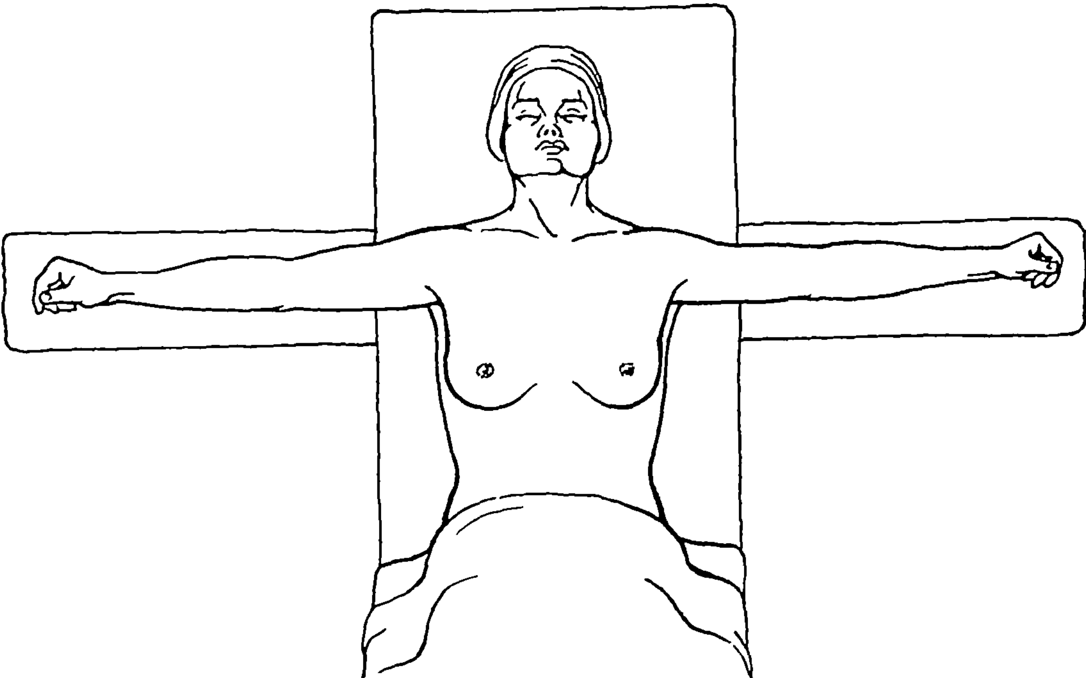


PLATE 2



PLATE 3

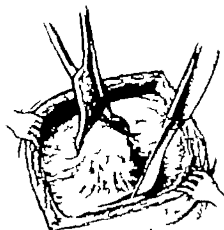


PLATE 4

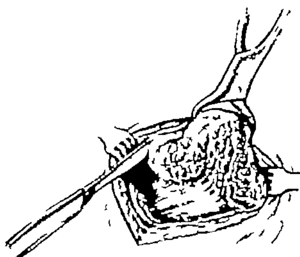


PLATE 5

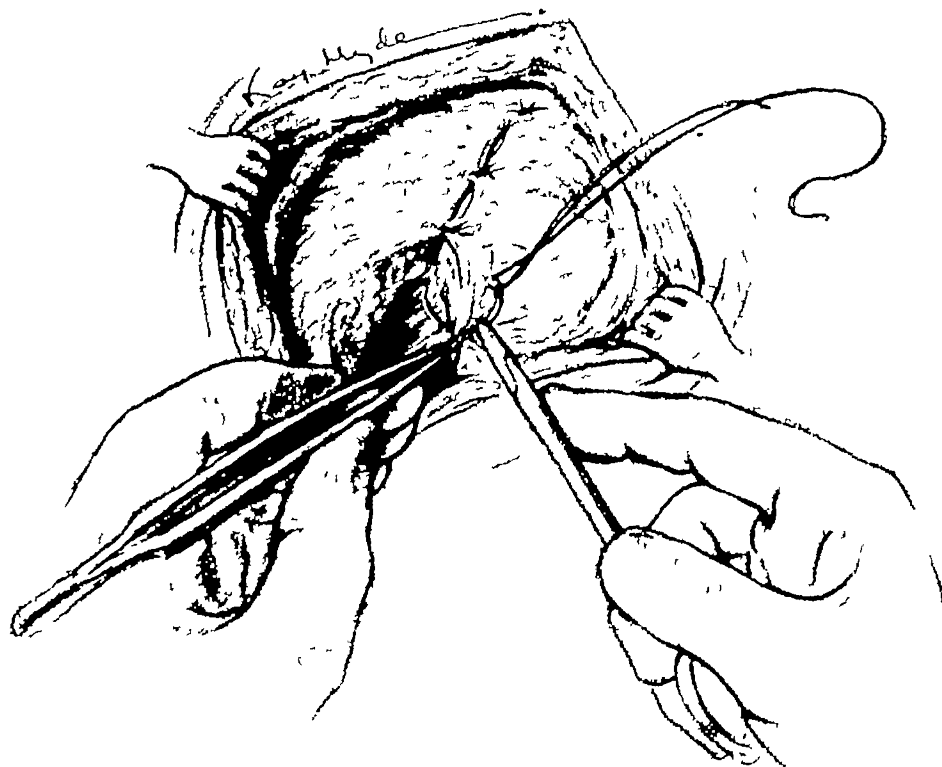


PLATE 6



PLATE 7

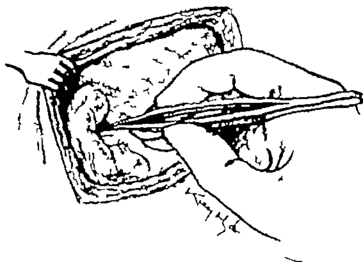
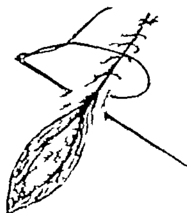


PLATE 8



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retraction of this type The specimen is dissected off the underlying pectoralis major muscle (Plate 4) so that one dissects beneath the involved area and removes all necessary tissue. A frozen section is performed immediately If the tumor is benign the wound is closed in layers (Plate 5) using fine vertical mattress sutures of silk on the skin. A small, soft rubber drain is placed at one end (Plate 6) and is removed the following day.

When the tumor removed is malignant, hemostasis is secured as usual, and the wound packed with a dry gauze pad (Plate 7) The skin is tightly sewn with a running, imbricating suture of silk which turns in the edges (Plate 8). The patient is then re-prepared, and re-draped, new instruments used, gowns and gloves changed and *an immediate radical mastectomy performed*

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MEDICAL TREATMENT OF CHRONIC CYSTIC MASTITIS

The growth and development of the ducts, glands and stroma of the breast, with the formation of a specific glandular pattern is under the influence of substances elaborated by the endocrine system The dramatic histologic and functional changes in pregnancy and lactation are related to the level of specific hormones in the body The less obvious changes that often take place in the menstrual cycle are also the effect of hormonal stimulation and probably the result either directly or indirectly of changes in the estrogen androgen balance The origin of these latter hormones in the ovary and the adrenal cortex, and the possible transformation from one steroid type to another is slowly being clarified In addition, the role of related hormones and chemicals in foodstuffs are often overlooked as factors that influence the level of these substances in the body

The organ in the body that regulates the level of most of the endogenous as well as the exogenous hormones, is the liver It contains the enzyme systems capable not only of transforming steroids of one type to another but also of metabolizing certain ones to an inactive state [1] In animal experiments it has been shown that the latter function is influenced greatly by the nutritional status, and that a major factor controlling the latter is the vitamin B complex as well as the protein content of the diet. In the animal deprived of vitamin B complex the liver no longer inactivates estrogen, but it continues to inactivate testosterone.[2,3] This leads to an alteration of the estrogen-androgen pattern in the body with the appearance of the so-called hyper-estrogen syndrome [4]

Patients with the hyper-estrogen syndrome have one or more of the following signs and symptoms premenstrual tension, cyclic mastalgia, cyclic focal breast hypertrophy lower abdominal bloating, menorrhagia, metrorrhagia, the feeling of impending menstruation and other related symptoms [4] The improvement of liver function with control of estrogen metabolism generally relieves most of these conditions within several months In many instances there may be undue target organ sensitivity limited just to the breasts so that they may undergo severe change in the premenstrual period with distinct lumpiness On the other hand, the process may be limited to just a lobe of one breast, and the engorgement and fulness may not occur at each period but at random periods The swelling may or may not regress completely between periods

Estrogen stimulation of the breast causes enlargement of the glandular lobules with an increase in associated connective tissue Over a period of time with alternating stimulation and regression the amount of connective tissue may slowly increase with a variable component of active glandular tissue Cysts will form, and a low grade inflammatory infiltrate is often superimposed In some patients a single poorly-defined nodule may become demarcated from the remainder of the breast parenchyma, in others, there may be multiple zones of palpable difference in each breast. The former condition is difficult to differen

tiate from an early carcinoma and if the examiner cannot be certain a biopsy is indicated Multiple masses are much more likely to be a hyperplastic process, but the possibility that one of them may be neoplastic should never be overlooked

These patients, if examined carefully, will have clinical evidence of nutritional deficiency Palmar erythema is an outstanding sign Many show cutaneous vascular spiders as well as easy "brusability" Changes in the tongue and lips are frequently noted The former may vary from thickening with loss of the fine granular mucosal papillations, to a flattened, atrophic, smooth tongue The corners of the mouth frequently show a crack which heals with difficulty Total body weight is rarely an index of the nutritional status of the patient, except in those rare instances when starvation is being carried out deliberately Liver function tests occasionally show slight impairment, particularly while the patient is in the mid-portion and second half of the menstrual cycle

Treatment of the liver to correct a hyper-estrogen syndrome, with particular emphasis on the nodular changes found in the breast, requires complete therapy over a protracted period [5] It is not always entirely successful, but deserves therapeutic trial Complete therapy means the administration of all of the presently known crystalline B vitamins, as well as an oral, whole crude liver preparation, and an increased protein intake in the diet In some instances yeast, yeast extracts or rice bran extracts may be substituted for the crude liver extract or whole liver Up to the present time, no one single factor in the vitamin B complex or in the crude liver brings about complete return of normal liver function and relief of the clinical picture It has also been found that unless all synthetic vitamins and crude liver are supported and supplemented by an increased total protein intake in the diet, there will not be a satisfactory therapeutic result The most effective preparation of liver is a desiccated, unfractionated powder This is taken orally in an amount equivalent to 40 gm of whole liver The synthetic vitamins include 36 to 45 mg thiamine, 21 to 36 mg riboflavin, 12 to 27 mg calcium pantothenate, 200 mg niacinamide, 3 mg pyridoxine, 210 mg choline, 27 to 150 mg inositol, 5 to 10 mg folic acid and 25 mcg vitamin B_{12} The liver and vitamin supplements are divided and given in 3 daily doses after meals In some instances, where gastrointestinal absorption is impaired due to long-standing nutritional deficiencies, parenteral therapy may be required and preparations containing thiamine, riboflavin, niacinamide, pyridoxine, calcium pantothenate and vitamin B_{12} are given intramuscularly in addition to the above. Injectionable liver extracts which contain only those factors soluble in water have been found to be ineffective and cannot be substituted for the oral preparations

It frequently will be necessary for patients to limit their total fat intake as they commonly have a tremendous stimulation of appetite on this regimen To prevent weight gain they are cautioned to limit fat and carbohydrate intake rather than protein intake A daily diet which includes at least 2 grams per kilogram body weight of protein and approximately 1 gram per kilogram of fat, with the remaining caloric intake made up of carbohydrate, will provide the minimum requirements

One of the first indications of the effectiveness of this therapeutic regimen is noted in women who are still menstruating They will state that the onset of menstruation "came without warning" and the customary abdominal bloating and premenstrual tension often disappear within a month of treatment. The cyclic mastalgia also diminishes in about that time and within two or three months is hardly noticeable The menstrual flow diminishes, and the number of days of flow decreases. In the older age groups where there has been some obesity there is a change in the configuration of the body with loss of fat around the hips, on the back of the neck and between the shoulders. The complexion becomes less muddy with less sebaceous secretion from the glands of the face particularly around the nose

Within two or three months bilateral diffuse lumpiness of the breast often disappears and painful nodules regress Occasionally lesions which contain cysts decrease in size, and sometimes the withdrawal of fluid from these cysts permits them to collapse and slowly be obliterated In some instances however a zone of thickening will remain and if there is any doubt concerning the nature of this lesion, it should be explored and removed Lesions of this type which have been removed and examined have always been composed of compact fibrous tissue in which there are a few atrophic ducts and small breast lobules It is necessary to maintain the patient on the nutritional regimen for long periods With complete regression of the nodularity of the breast, the intake of crude liver and synthetic vitamins may be halved Studies have shown[4,5] that if treatment is terminated, recrudescence of the lesions frequently takes place Subsequently the same therapy may not be quite as effective

This method of treatment is not a panacea nor is it intended to replace surgical biopsy when indicated. After biopsy has been performed and the diagnosis accurately established, it may be worthwhile to proceed with a course of medical therapy as outlined. Its greatest usefulness seems to be in young women whose chief complaints are mastalgia, and other early signs and symptoms of the mastitis syndrome (*see* p 19) It is lacking when the disease process is advanced or irreversible, which is the more dangerous clinical form and the stage when biopsy is more imperative

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CHRONIC CYSTIC MASTITIS AND CANCER

The relationship of chronic cystic mastitis to cancer has varied widely among different investigators. Ackerman and del Regato[1] stated that it is "directly proportional to the liberality of the pathologist in diagnosing such a lesion." Foote and Stewart[5] similarly have stated that "the concomitant occurrence of cancer in so-called chronic cystic mastitis will vary statistically according to the selection of lesions."

By and large, pathologists have agreed that the microscopic changes of small cyst formation and proliferation of the epithelium occur in a large percentage of cases of cancer of the breast. MacCarty and Mensing[8] found 100 per cent of 967 carcinomas of the breast associated with chronic cystic mastitis. Ewing[4] reported at least 50 per cent, Semb,[9] 80 per cent. Cheatle[3] repeatedly emphasized the association of cancer and chronic changes in the breast.

Pathologists have differed with regard to the direct etiologic relationship of these changes to carcinoma. Ewing[4] and Warren[10] both used the term precancerous and thought that epithelial hyperplasia preceded cancer in enough instances to be significant. However, Foote and Stewart,[5] after an exceedingly careful and critical analysis of 200 cancerous and 300 noncancerous breasts, found that the changes described in chronic cystic mastitis are just as common in noncancerous as in cancerous breasts. They further state that it has not been proved that these changes are the focal starting points for cancers of the breast in any sufficient number to be significant. This appears to be the conclusion of more recent reports. Hendrick[6] operated on 484 patients with cystic disease of the breast and made follow up examinations on 91 per cent. He states the incidence of carcinoma was no greater in this group of patients than in the general female population. Such a conclusion is also the experience of the author who in a ten-year study of clinic and private patients can determine no greater incidence of cancer in patients with a chronic cystic mastitis syndrome.

Confusion exists over the criteria which different pathologists use to diagnose chronic cystic mastitis. In Foote and Stewart's[5] material 59 per cent of the patients with cancer of the breast exhibited one of five cystic and proliferative lesions, cysts, papillomatosis of the duct, blunt duct adenosis, sclerosing adenosis and apocrine epithelium. Sixty-five per cent of 200 noncancerous breasts likewise contained one of these five features. When two or three of the foregoing features were tabulated in the two groups, the difference between the cancerous and the noncancerous breasts was not outstanding, and the etiologic relationship of chronic cystic mastitis to cancer was not proved.

As the foregoing statements would indicate, there has been a steady tendency to regard these lesions as not necessarily leading to cancer. Starting with Bloodgood,[2] then White,[11] Lewis and Geschickter[7] and, more recently, Foote and Stewart,[5] to mention a few authors, the realization has grown that present

information is not conclusive enough to state with exactness the precancerous nature of this lesion

Unfortunately and despite the weight of evidence to the contrary the practicing physician is under considerable pressure to treat occasional advanced cases of this disease in a near radical manner that is, by simple breast amputation. Most surgeons of experience see a frequent association between advanced mastitis and breast cancer *in the operating room* Confronted with a previous mastitis history and a fully developed histologic mastitis in the breast it is understandable why the surgeon may feel the disease is "pre-cancerous" Although anatomic and scientific studies deny the existence of any pre-cancerous condition the conscientious, practicing surgeon, on the basis of what he sees in the operating room may with some justification treat this disease by removal of all breast tissue unilateral or bilateral. Not that this is a recommended procedure it is not but it emphasizes the fact that there is a disparity between two groups the clinicians and the pathologists Lending some support to the clinical group are the studies of Warren[10] who in a careful and extensive clinical study followed 1,206 patients with chronic cystic mastitis Cancer developed in 42, or about 3 times the incidence expected in the normal population More concretely between the ages of thirty and forty nine women with chronic mastitis have 11 7 times greater incidence of cancer After fifty years of age the incidence is 2.5 times greater It is still believed, therefore despite the lack of anatomic evidence that the proliferative lesions of chronic cystic mastitis predispose toward a slightly higher incidence of cancer

Recommended treatment, nevertheless, is excisional biopsy of the area in question Close follow up examinations are necessary It is felt that if carcinoma does develop it can be detected in an early stage and prompt treatment administered

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PAPILLOMAS OF THE DUCT

What to do with the patient who exhibits occasional bleeding from the nipple in the absence of a palpable tumor is still a perplexing problem and much disagreement exists on the extent of surgery necessary to treat this condition properly. In studying total hospital experience several authors have found that about 50 per cent of the patients who have bleeding from the nipple also have breast cancer.[1,10,16] However in other more recent articles[6,9] the reported incidence of carcinoma associated with nipple discharge is far less. All degrees of incidence from 5 to 70 per cent have been reported.[9] There is a difference, too regarding the incidence of cancer in those breasts with or without a palpable tumor. The problem for the practicing surgeon is naturally greater in that group of patients where no tumor is felt. In the palpable group biopsy is promptly performed and the question settled.

It would appear both on the basis of personal experience[13] and the literature[2,4,9,11,13] that the incidence of cancer in the breast in those patients showing nipple discharge but no palpable tumor is very low, probably 1 to 2 per cent or less. Treves,[17] in a study of all carcinomas of the breast found 2 per cent of 1000 cases who had bleeding from the nipple as their first symptom. It is also felt that the truly sanguineous discharge may possibly be more important regarding cancer than the non bloody serous or turbid type which is more common and seems to be even less significant clinically. However Axelrod[2] takes issue with this. Fleming and Drosd[3] found bloody discharge only in breasts having papillomas. Bloodgood[3] felt that discharge, either bloody or serous usually indicated an intraductal papilloma.

Nevertheless, many consider bleeding from the nipple a grave symptom, certainly the patient does and in the past breast amputation had been frequently recommended. The vast majority of patients however who have bleeding from the nipple do not have cancer and a conservative method of treatment may be carried out with safety. This is especially true when bleeding occurs in the absence of a palpable tumor.

In general, one might discuss four types of bleeding from the nipple. First, bleeding may occur with a large hard, palpable mass that clinically resembles cancer. Second, the bleeding may be associated with a mass that is more characteristic of chronic mastitis. Third, the bleeding may come from a small palpable tumor usually in the periphery of the areolar region, which contains a papilloma; such an area often transilluminates darkly because of contained blood and the tumor is easily localized by palpation. The fourth type, which frequently presents diagnostic difficulty and is of chief concern, is slight bleeding from the nipple in the absence of a palpable tumor. Such patients may complain of bleeding for only two or three days during the year occasionally occurring after slight trauma on examination. Pressure at one point about the periphery of the nipple

usually produces bleeding, but the localization of the tumor is not always easy or accurate, since in many of these cases bleeding may be produced with pressure over half of the areolar circumference or over a large portion of the breast Furthermore, significant information is not always obtained in these patients by transillumination

Because of the difficulty in localizing this group of tumors, amputation of the breast, rather than local excision, is frequently recommended When the excised tumor is examined microscopically, it proves in most instances to be a small duct papilloma, entirely benign Another indication frequently cited for mastectomy is the multiple nature of these papillomas By roentgenographic studies of the breast after the injection of a radiopaque oil into the nipple ducts, Hicken[7] found that in many instances papillomas involved all of the mammary tissue Foote and Stewart[6] studied generalized duct papillomatosis, among several other histological features, in 300 cancerous and 200 noncancerous breasts Using as their criterion "all stalked papillary adenomas, usually macroscopic," in the large or medium sized ducts, they found that the incidence of papillomatosis was approximately the same in cancerous (36 per cent) as in noncancerous (29 per cent) breasts In the age group between forty and fifty years, the frequency was identical in the two series (40 per cent) As a matter of fact, these investigators found that macroscopic papillomas were more characterisic of benign rather than of cancerous breasts, and the multiplicity of the lesions showed no significant difference in the two groups They concluded that "Although it is rare to find any early duct cancer of the breast in the absence of a typical papillomatosis, the actual number of papillary lesions that eventually become mammary cancers must necessarily be a very minute fraction, and we know of no way to prognosticate the probable course of any given histologic type"

Despite these reassuring opinions regarding the nature of the lesions causing nipple discharge it has long been known that any bleeding from the nipple should be carefully investigated and its exact cause established Any intraductal papilloma of the breast should be excised surgically even though the bleeding or discharge may have ceased, for such a tumor may continue to grow even in the absence of symptoms When an intraductal papilloma is removed, and subjected to histologic examination it is usually always benign and shows no infiltration beyond the duct epithelium (*see* Figs 2 and 3, pp 14 and 15) Therefore, treatment should be aimed merely at removing the palpable tumor In those instances where no tumor is felt but where pressure over a zone or area yields nipple discharge one is justified in removing a wedge or block of tissue, usually subareolar, from such a region and examine it histologically for malignant change Where a palpable tumor is present removal of this alone is all that is necessary

Some years ago, in order to find the exact location of a non-palpable papilloma, Hicken[7] described a method of localizing duct papillomas in which a contrast

medium (Thorotrast) was injected directly into a large terminal duct of the nipple. This diagnostic procedure has not become popular in spite of the fact that Hicken stated that in more than 300 such examinations he had encountered only three or four untoward reactions in the early part of his series. The method was criticized by Romano and McFetridge[13] who found granulomas necrosis and edema in 4 of their 23 patients Furthermore, Sowers and Masson[14] reported a case in which fat necrosis following the injection was of sufficient magnitude to warrant mastectomy

Such a refinement has become wholly unnecessary The areolar pressure test localizes a zone of involved tissue and removal of this is more adequate therapy than carefully dissecting out one main duct alone

In those instances where a tumor is not palpable and the pressure test fails to localize the involved zone the patient is instructed to leave the breast entirely at rest; and to wear a brassière continually After one week she is asked to return Frequently by that time the small ducts will have filled with enough secretion to be palpable and yield nipple discharge on pressure Should no discharge be elicited the patient is instructed to return at regular intervals until the exact area or zone is located. Local surgical excision is then performed

Surgical Technique of Resection of Duct Papillomas

The patient is placed supine as in Plate 1 A circumareolar incision is made just beyond the areolar margin (Plate 9a) and following one half of the circum ference of the areola In patients with a draining sinus tract a curved, elliptical incision is made which excises the sinus opening (Plate 9b) The nipple and areola are dissected backwards by undermining, and the opposite edge also is released (Plate 10) The nipple and areola are dissected back almost completely preserving about half of the nipple duct system The subareolar ducts and the involved duct and papilloma can be visualized (Plates 10 and 12) A sagittal view is seen in Plate 11 A diamond shaped wedge of breast tissue is dissected free (Plate 12) This is facilitated by grasping the area, not the tumor in a towel clip and retracting it upwards The specimen is removed and submitted for frozen section analysis If benign as is usually the case, the deep layers are closed (Plate 13) and the skin drawn together with fine vertical mattress sutures of silk (Plate 14) A small, soft rubber drain is placed at one end, and removed in 24 hours

The amount of breast tissue removed, and the extent of the duct system resected, will depend entirely on the size of the tumor and the degree of breast tissue involvement. The exposure gained with this incision can, of course, be more limited with resection of only the involved duct. Because papillomatosis is a generalized process and the involved duct not always clearly defined, this is rarely possible

PLATE 9

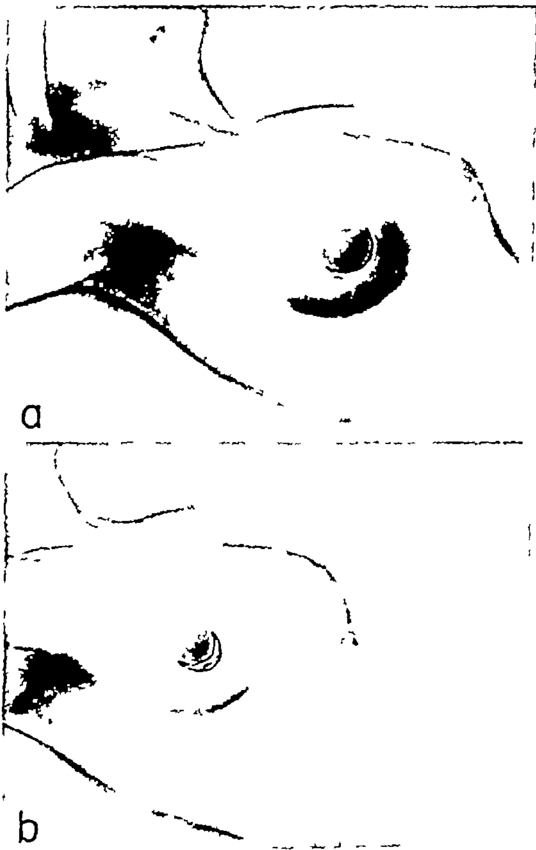


PLATE 10

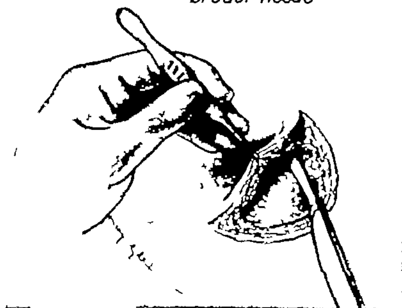


PLATE 11

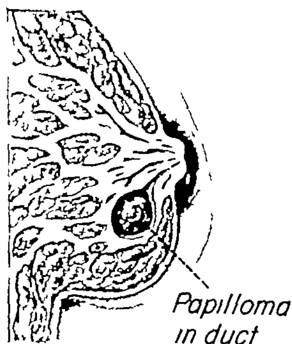


PLATE 12

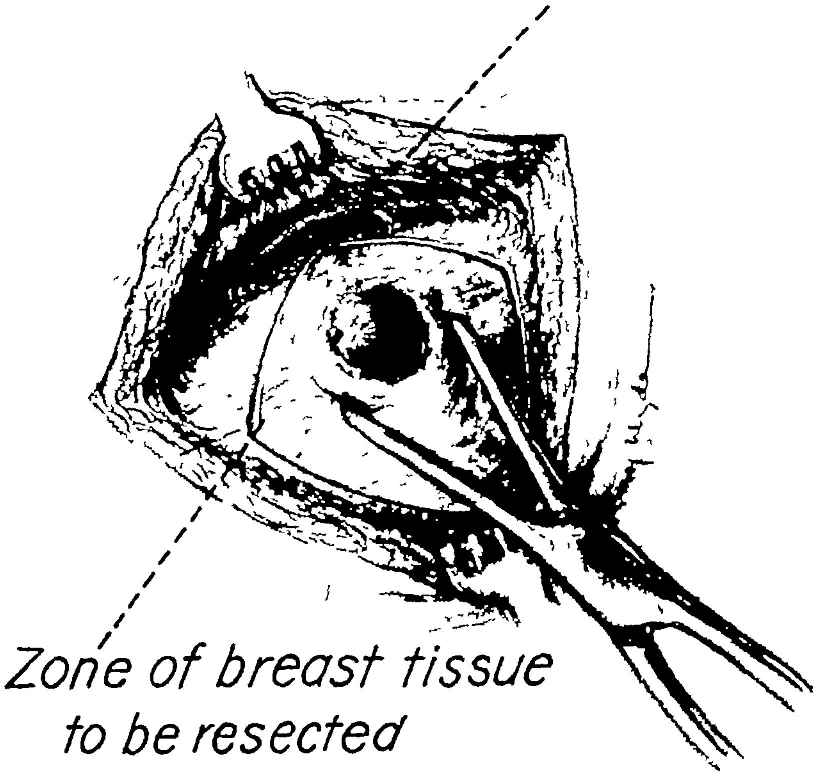
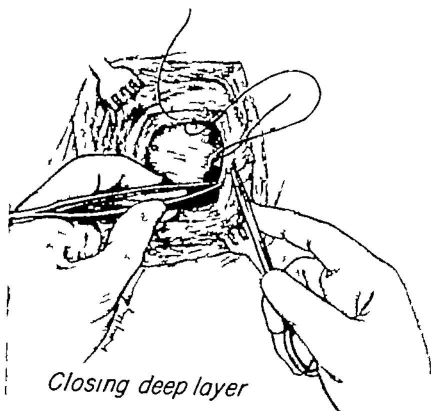

Nipple and areola
undermined
Zone of breast tissue
to be resected

PLATE 13



Closing deep layer

PLATE 14

Skin closure with small soft drain



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FIBROADENOMAS

Tumors of this type have several distinctive characteristics, hence diagnostic difficulties are considerably less than with chronic cystic mastitis or intraductal papillomas As with other kinds of mammary tumors the upper outer quadrant is the most common site In the majority of patients the first symptom is merely the presence of a lump in the breast Rarely will pain be associated with the tumor They are freely movable, well outlined and firm without tenderness Occasionally they may grow to large size. Not infrequently there is a history of prolonged duration without appreciable change When asked why they let it go patients usually answer "because it did not bother me."

The majority of these tumors occur in females between the ages of twenty and thirty nine although patients over sixty and under twenty may show such tumors In Geschickter's[2] series 8 per cent were beyond the menopause and in 10 per cent the tumors were present before the first menses

In a study of 26 patients with this tumor[3] 8 had associated gynecologic complaints. Three had fibromyomas of the uterus, one of them having a thyroid adenoma as well Three had menstrual irregularities and 2 were experiencing symptoms of the menopause The relation of this tumor to periods of estrogen stimulation has been commented on by several authors

Fibroadenomas occur predominantly in women of the child bearing period The tumors are liable to rapid growth during pregnancy and also when they occur at the time of the menopause This is reason enough for early local excision In addition, malignant degeneration is not uncommon Of 29 sarcomas of the breast collected by Geschickter[2] 11 were thought to have formed from preexisting fibroadenomas Adair and Hermann[1] collected 30 sarcomas and believed that 4 were from previous fibroadenomas Cystosarcoma phyllodes (giant intracanalicular fibromyxoma, giant mammary myxoma) is an old term denoting a large, slowly growing solitary tumor of the breast, considered to be benign. It is felt that these tumors also arise from preexisting fibroadenomas and may become malignant (*see* section on cystosarcomas, p 42) which further emphasizes the importance of excising a fibroadenoma. As with any other breast tumor excision and histologic examination is the only way to assure certainty of diagnosis. Although these tumors are relatively easy to diagnose clinically in an occasional instance the tumor may be hard to differentiate from cancer without microscopic study

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CYSTOSARCOMA PHYLLODES

Since 1838 when Johannes Muller[8] gave the term cystosarcoma phyllodes to a large, bulky mammary tumor, and described its peculiar gross and microscopic features, it has been known by at least 26 other appellations ranging from "hydated tumor of the breast"[13] to "giant intracanalicular fibroadenomyxoma."[10] During the past fifteen years this tumor has become more readily recognized as a distinct entity In 1931 Lee and Pack[5] published an excellent and exhaustive review of the literature on this tumor They collected 105 cases and added 4 of their own Since then others[2,6,7,9,10,12] have shown much interest in the subject and added additional cases to the literature It is quite evident that Muller[8] and



Fig 6 Patient with cystosarcoma phyllodes revealing huge size, overlying dilated veins, but lack of skin involvement

other early writers encountered much later stages of these neoplasms than are now commonly seen. The early reports make great note of the large bulky size of the tumor which could only have reached such proportions after long neglect (Fig 6). When in this stage it is quite diagnostic.

The majority of these tumors appear in women in the premenopausal age group but extremes of fifteen and seventy nine years of age have been seen. The tumor is firm and freely movable. When it attains huge size numerous dilated veins may be seen coursing through the overlying skin. It is nontender and unattached. If not very large it cannot be distinguished clinically from a tense cyst or fibroadenoma. On palpation it has a rubbery firm feel with clear and distinct margins. There often is a history of a preexisting tumor probably a fibroadenoma, which suddenly became much larger. Lactation frequently is associated with the rapid increase in size. Foote and Stewart[3] have recently pointed out that the tumor need not necessarily be of large size and that small tumors present the coarse, intracanalicular protrusions and connective tissue cellularity seen in the large ones.

Grossly the tumor tends to fall apart because of the enormous clefts and polypoid masses (Fig 7). These are placed intracystically and referred to as

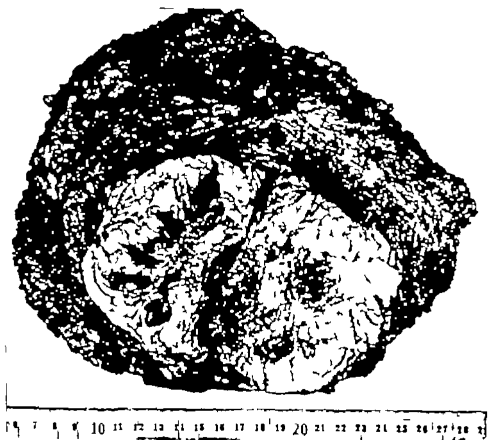


FIG 7 —Gross appearance on cut section showing enormous clefts and polypoid masses intracystically placed

"papillary elephantiasis."[5] These masses may fill the clefts so well that they simulate a solid tumor. The tumor may be multilocular and the cysts often confluent due to rupture of the intervening septa. A thin straw-colored fluid is found within each cyst but at times the secretion may be mucoid or gelatinous. The stroma is usually myxomatous, loose and hemorrhagic and of a grayish-white, glistening appearance. Most of the tumors are well encapsulated, but some may be covered by a thin transparent membrane. The tumor is not invasive and does not destroy the surrounding breast tissue.

Muller,[8] in his original description, states that "the extraordinary forms which cystosarcoma phyllodes assumes, at once suggest the notion of its cancerous nature, and yet, the disease is perfectly innocent and as far removed from carcinoma as are those nonsuppurating cauliflower condylomata of the penis, and of the female genitals, which have so often been mistaken for cancerous structures" (*See* Fig. 5).

Recent reports[2,11,12,14] however, have shown that all of these tumors cannot be considered "perfectly innocent." A small percentage become very malignant with rapid and widespread metastases and death. Each of these tumors is a potentially malignant growth and deserves prompt surgical extirpation. It is best to refer to them as "benign" or "malignant" cystosarcoma phyllodes. In addition, if, as Lee and Pack[5] state, they arise from preexisting fibroadenomas the surgical removal of those very common and innocuous tumors takes on added importance.

It has been stated that the tumor often is present for a long period in a quiescent phase. Sudden increase in size within a short space of time is frequently reported[5] with the history of initial onset going back many years. This would appear to be true of the large, bulky lesions, but not so true of the smaller ones. A personal study showed that over half of the patients with benign tumors had them for only one year, the majority for only six months. A similar time sequence is seen with the malignant variety.[12] One may then look with some doubt on the theory of sarcomatous change of a preexisting tumor. It may be just as probable that when malignant these tumors are so from their inception.

The malignant variant of cystosarcoma phyllodes is a very dangerous tumor. Metastases are widespread and dissemination is rapid because of its vascularity. Spread, therefore, is usually by the blood stream. Axillary lymph nodes do become involved but at that time blood borne metastases have also occurred. This observation is similar to that of others[1,2,4,12] although Cooper and Ackerman[2] reported a case with axillary metastases and invasion of the underlying pectoralis major muscle.

In treating the benign tumor complete local excision is adequate. If the tumor is huge this may require simple mastectomy. Treatment of the malignant variety is not so easily dismissed. Because of its rapid invasion of the blood stream, and the fact that lymph node metastases probably occur after this has taken place, simple mastectomy should be just as effective as radical mastectomy.

In the occasional patient though, with axillary lymph node metastases or pectoral muscle involvement, and no other evidence of disease one would feel radical mastectomy indicated. Nevertheless, knowing the method of metastases, the frequent lack of lymph node involvement, the freedom from local invasion and the widespread dissemination one feels that the malignant variant of this tumor is one of the few indications for simple mastectomy

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MISCELLANEOUS TUMORS

Lipomas.—Although lipomas are completely innocent tumors their presence alone may cause much worry and anxiety. It may be difficult to be certain that they are only lipomas. The majority occur in patients between forty and fifty years of age. The tumors vary in duration, and some show progressive increase in size. Most occur in the upper quadrants of the breast. They are soft, superficial and frequently lie on top of the mammary tissue. They are unattached, freely movable and, with few exceptions, nontender. Occasionally some are firm, tender and attached to the skin. The average size is 3 to 4 cm. Men are not infrequently involved. If gynecomastia is excluded, lipomas are the most commonly observed benign tumors in the male breast. Local excision should be performed in each case.

Fat Necrosis.—Recognition of this peculiar condition is important because it mimics carcinoma. There is usually a history of injury, but occasionally the patient will have forgotten about the traumatic incident or not be able to recall it accurately. A few days to a week later a lump will be noticed which may or may not be associated with an ecchymosis. It may be nontender, and as observed will not increase in size but may become more firm. On examination one feels a solid tumor, not freely movable and with a suggestion of induration. Local excisional biopsy is the treatment of choice. A clinical diagnosis of fat necrosis is naturally made easier in the presence of ecchymosis, yet one must also consider the coincidental finding of cancer in an area of injury. Therefore, even in these instances excisional biopsy would be best when a definite tumor persists more than a week or ten days. Although the author feels that trauma to the breast has no etiologic significance relating to the cause of cancer, one cannot avoid the medicolegal relationships involved. When cancer is coincidentally found nothing can shake the conviction from the patient's mind that it was caused by the injury.

Accessory Mammary Tissue.—Such tissue presenting in the extreme tail of the breast, near the axilla, may show a confusing picture. Some patients have bilateral masses in the tail of each breast. Soreness and tenderness may bring their attention to this area. On examination one finds soft, bulky, slightly thickened, poorly outlined masses near the axilla. One side may be more pronounced than the other. As a rule no treatment is necessary. If a tumor is palpated it should be removed for biopsy. There is no evidence that tumors in this region are any different or more frequently malignant than in other areas of the breast.

Chapter 4

GYNECOMASTIA

If this is a truly neoplastic condition it is probably the most common tumor seen in the male breast[6] It is a benign lesion in which the male breast is enlarged, and often painful, and is seen in all age groups The peak age incidence varies according to reported authors in Menville's[5] series thirty-one to forty years of age in Karsner's[4] twenty-one to thirty in Jaaskelainen's[3] also twenty-one to thirty and in Sirtori and Veronesi[6] fifty-one to sixty In the author's experience it has been seen predominantly in the thirty to forty year-old group It is seldom seen before age ten Secretion from the nipple, usually serous rarely sanguineous, though commonly seen when the tumor is caused by hormone alteration, is not a prominent feature of gynecomastia occurring without evidence of other disease

Two forms of the disease are described The first type occurs spontaneously without hormonal relationship the second occurs as a related finding incidental to disease in another part of the body The latter type is more frequently bilateral and is seen in conditions where the normal endocrine balance has been altered. This situation would occur after the administration of estrogens for the treatment of prostate cancer in conjunction with liver disease with testicular lesions, primarily those causing atrophy or in hormone producing testicular tumors, and in chronic, debilitating systemic disease and malnutrition The diagnosis in this group is more apparent and the factor of ruling out carcinoma is less acute

In the nonhormonal, or spontaneous group the lesion is more subtle. It is usually unilateral and a history of one to three months duration is frequently given Nipple secretion is rare and pain is mild A disconcerting feature is a small, hard, disk or button like tumor felt directly beneath the nipple and areola which on firm palpation may be quite tender The breast is moderately or greatly enlarged and the tissue shows a diffuse, mild thickening and infiltration which is easy to differentiate from mere fatty infiltration Axillary node enlargement is not present.

It is this form which the surgeon is called upon to treat so that he can rule out the presence of cancer by excisional biopsy It should include the subareola, disk like tumor Many patients are also concerned because of the cosmetic factor and it is safe to say that surgery is performed as much for this reason as to rule out cancer The condition however is a reversible one in some patients, and

unless the diagnosis is in doubt or the appearance a factor of major concern, these patients are best left to routine follow up examinations without surgical intervention

Despite the separation of gynecomastia into two general groups qualitative differences between unilateral and bilateral gynecomastia or between hormonal and nonhormonal gynecomastia have not been observed[6] The etiology of the condition is obscure but it is fashionable to claim as a cause a hormone imbalance marked by either an excess of estrogens or androgens Even in the nonhormonal group the condition could be due to an imbalance that cannot be detected with the most sensitive criteria available today In a considerable number of patients gynecomastia arises during liver disease, malnutrition, and chronic debilitating illnesses all conditions related to the poorly understood entity called hyperestrogenism[1,2] In the latter the diseased or "sluggish" liver cannot inactivate estrogens which in turn affect breast tissue Some patients with gynecomastia do respond to crude liver extract and vitamin B complex (*see* p 28) and in the selected case such a trial is considered worthwhile Best results with this form of treatment occur in boys at the age of puberty

Surgical Technique of Treating Gynecomastia

The patient is placed supine on the table with the arm extended at right angles (Plate 15) An incision is made which surrounds the areola on one-half of its circumference and is extended outward for 2 cm on each side (Plates 15 and 16) The nipple, areola and adjoining tissues are undermined completely forming an inferior flap (Plate 16) The same is done in the opposite direction, exposing the entire underlying breast tissue (Plate 17) Using a large towel clip (optional) the breast tissue is grasped (Plate 17), held upward and dissected free The button-like tumor is encompassed in the grasp of the towel clip but not penetrated. The breast tissue is dissected off the underlying pectoralis major muscle which forms the floor of the dissection (Plate 18) The specimen is submitted for frozen section analysis If benign, the deep tissues are approximated (Plate 19), and the skin edges sewn together with vertical mattress sutures of fine silk A drain is placed at one end of the wound (Plate 20) It is removed the following day

PLATE 15



PLATE 16

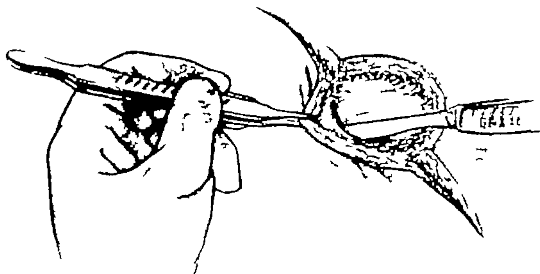


PLATE 17

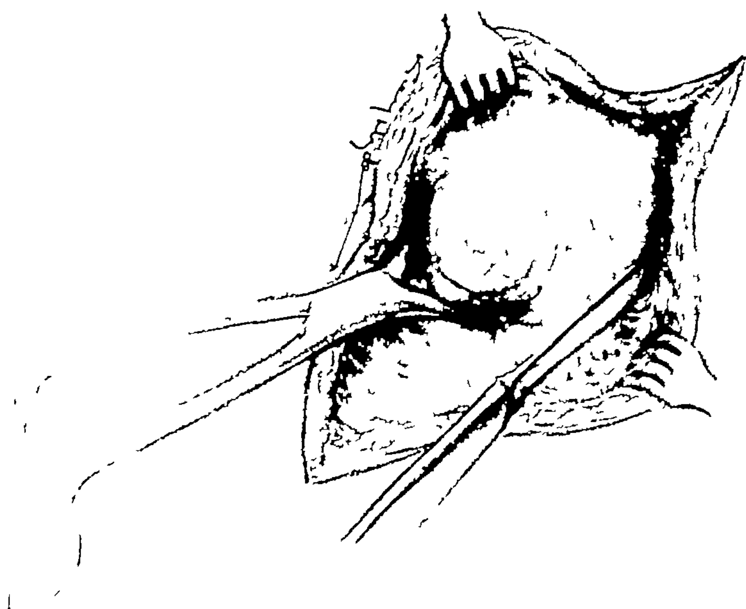


PLATE 18

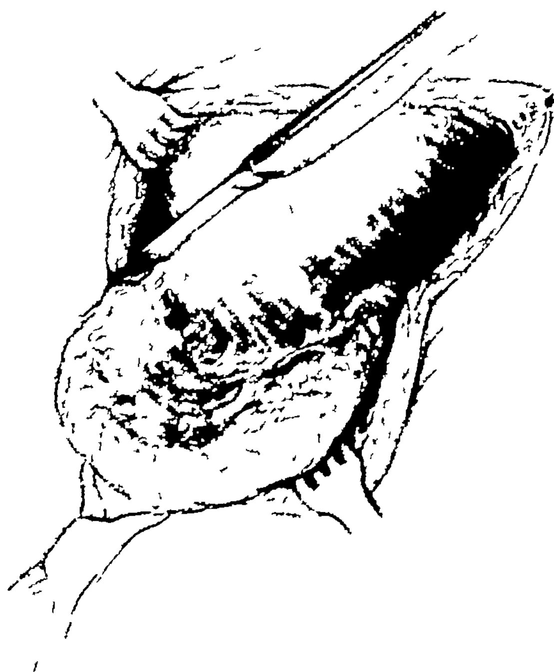


PLATE 19

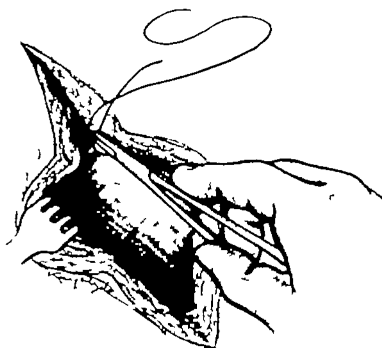
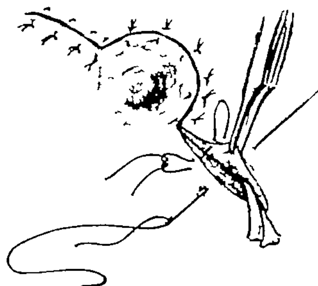


PLATE 20



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Chapter 5

SPONTANEOUS ABSCESSES AND DRAINING SINUSES

This condition is frequently seen in men, especially if the source of abscess is actually the glands of the overlying skin rather than the breast tissue. Incision and drainage is all that is necessary as they resemble abscesses elsewhere in the body. In women, abscesses will develop spontaneously on the basis of chronic cystic mastitis. Intense engorgement and thickening of the duct system with extravasation of intraductal secretions into the surrounding breast tissue with secondary infection will cause a major abscessed condition. These occur with or without lactation. Spontaneous rupture will often occur especially if the abscess is near the nipple or areola margin. Persistent, draining sinuses develop and in some patients continue for years. After incision and drainage, antibiotic therapy and other ancillary measures, such as compresses, most abscesses disappear. However, where a persistent sinus remains, complete local excision of the entire involved area seems to be the only treatment which will suffice. When the sinus tract is near the nipple, excision must include the underlying tissue in this region, sometimes extending directly upwards into the nipple itself, as the infected, granulomatous focus may lie hidden in the base of the nipple. Efforts to recover acid fast bacilli, fungus or other esoteric organisms from the tract have met with failure. The involved area is only moderately painful, usually will discharge intermittently for a few days, then disappear, only to recur again in another week or two. It is problematic whether the discharge increases or decreases with the ovarian cycle.

Surgical Technique of Treating Draining Sinuses

In the large majority of patients, draining sinuses treated as described under Papillomas of the Duct (page 35) heal without incident. Excision must be generous and include tissue at the base of the nipple. In rare cases there is persistent drainage despite adequate local excision. This is a source of much anxiety and annoyance to both patient and physician. When extreme, a resection of the entire areola and nipple duct system may be necessary. The technique of this procedure is outlined in the accompanying diagrams.

An elliptical incision is made which surrounds the entire areola and nipple (Plate 21a) and extends across the dependent portion of the breast. The skin edges are undermined and the deeper tissues incised (Plate 21) down to the

PLATE 21

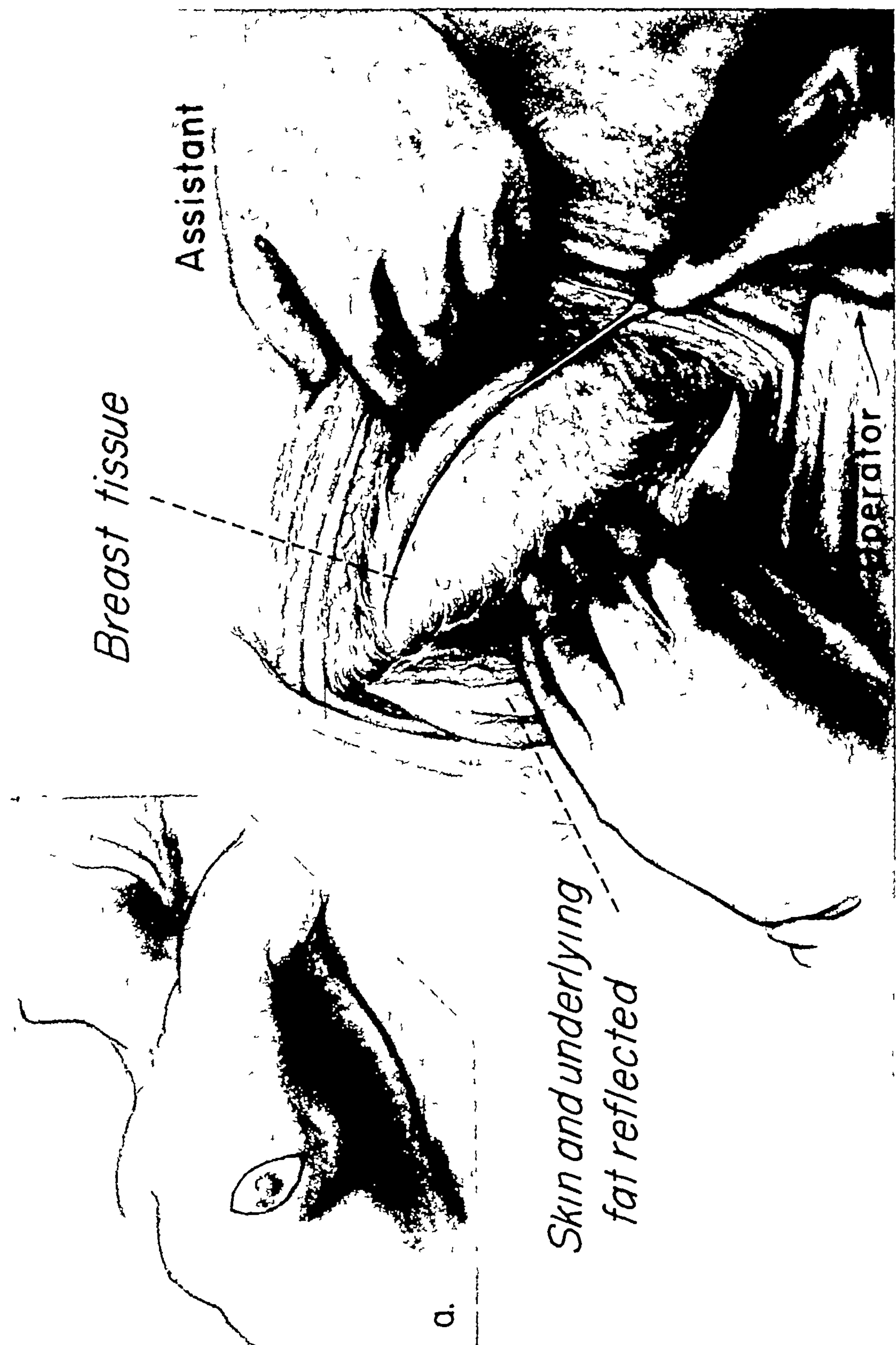

Assistant
Breast tissue
Skin and underlying
fat reflected
a.

PLATE 22

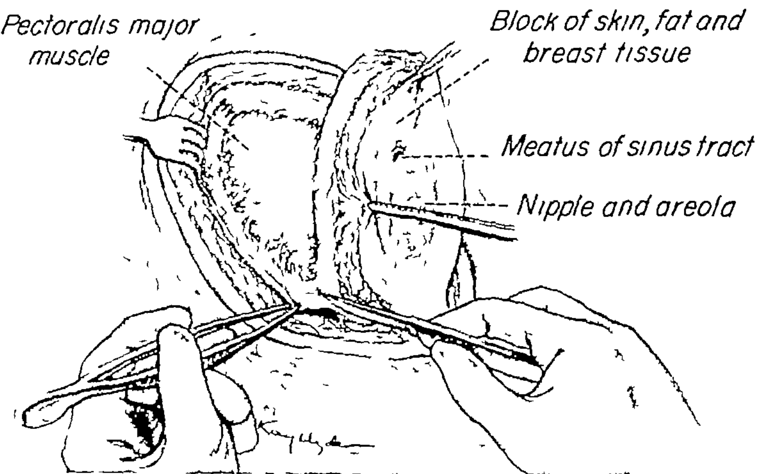

Pectoralis major muscle
Block of skin, fat and breast tissue
Meatus of sinus tract
Nipple and areola

PLATE 23

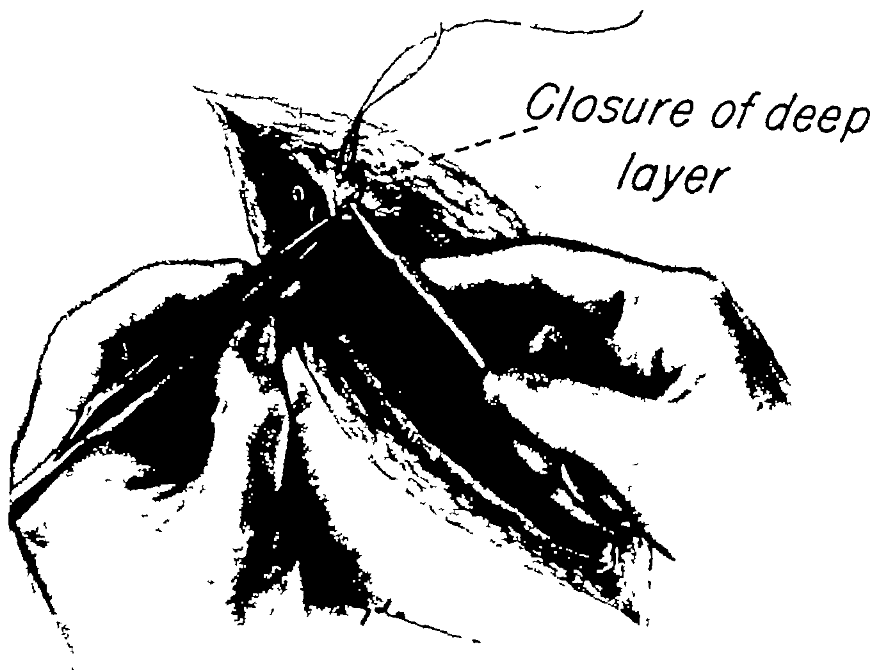
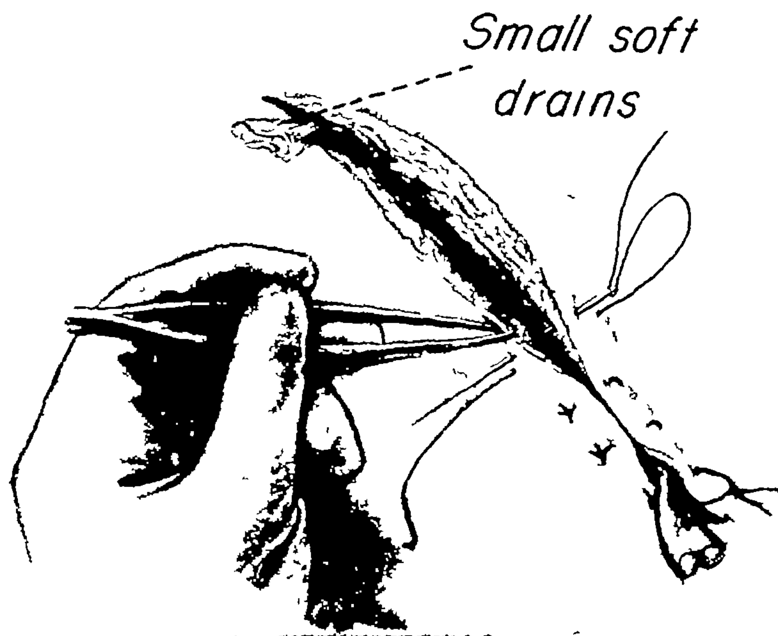


PLATE 24



pectoralis major muscle (Plate 22) A large block of involved tissue is removed (Plate 22) Frozen section examination is made to determine the exact nature of the diseased tissue If benign the deep layers are closed (Plate 23) and vertical mattress sutures of fine silk are used on the skin Small soft rubber drains are placed at both ends of the wound (Plate 24)

Although the possibility of cancer is rare in patients with persistent draining sinuses it should be kept in mind, and a radical mastectomy performed immediatly when indicated. For this reason frozen section examination is made on all breast tissue excised

Chapter 6

BREAST CANCER

THE voluminous studies on cancer of the breast point to its intense interest on the part of surgeons, internists, endocrinologists, pathologists and radiologists. Throughout the past half-century there have been recurring episodes of renewed study of this disease. At the present time, through the provoking report of McWhirter[26], there is another flurry of re-evaluation, review of techniques, and conscientious soul searching. Recent innovations of Urban[38] and Ariel[4] improving and enlarging on the classical radical mastectomy of Halsted[11] present a new challenge in judgment and technique to the surgeon. There also has developed a more basic interest relating to the physiology and endocrinology of breast cancer, stimulated by the work of Huggins[16,17] on the adrenal glands and of Luft and Olivecrona[21] on the pituitary.

Notwithstanding all this, paramount interest to the practicing surgeon still lies in early diagnosis and treatment. These two factors remain all important despite the valuable report of MacDonald[25] on biologic predeterminism of human cancer, which points out the very variegated pattern of mammary carcinoma. It would seem that for this very reason early treatment and diagnosis were of primary concern. The fact that cancer of the breast despite much lay education, still remains the second greatest cause of death from cancer among women should call for redoubled efforts.

Admittedly, there are patients with breast cancers that cannot be cured by any method. On the other hand, there are many who carry a poor prognosis because they have advanced disease when first treated. Since the majority of breast cancers adhere to a known pattern and life history, early diagnosis and treatment still will enhance the outlook. Certainly the surgeon confronted with a suspicious breast lump cannot delay biopsy. Even though the fair and erudite, statistical report of Lees and Lees[20] may show that all our efforts in the treatment of breast cancer do not alter the survival rate, to the patient with a lump in the breast, and to the many patients surviving decades after their treatment, the surgeon's efforts are of vital practical concern. On the basis of personal experience and published reports[1,7,31] early diagnosis and treatment are recommended as factors favoring prognosis, and until a truly workable, physiologic cure for mammary carcinoma is discovered radical mastectomy, of the type developed by Halsted, remains the preferred method of treating breast cancer. One may infer from

this that mammary cancer in women has been conquered and all surgeons concerned satisfied with the results. Nothing could be farther from the truth. Elsewhere in this book appear other methods and techniques which strive to show how results may be improved and morbidity curtailed.

Diagnosis

There are several factors other than physical characteristics which are of help in determining the nature of a breast nodule. Paramount among these is the age of the patient. Cancer is most commonly seen between the ages of forty and sixty; it is infrequently seen in women below thirty five and occurs less frequently in women who still have normal ovarian secretion.

Large statistical studies[7] show a higher mortality rate from mammary cancer in single women over thirty years of age than in married women. The incidence of breast cancer in married women is higher in those who have never borne children. In those women who bore children there is a higher incidence of breast cancer in those who did not nurse them. Patients who have had previous benign tumors, fibroadenomas, cystic disease and duct papillomas, show a higher incidence of subsequent cancer on statistical studies (*see* p. 31). The influence of heredity on breast cancer is debated, but the presence of breast cancer in mother and then daughter is not unusual and deserves emphasis. Of the many factors which are of etiologic significance in the causation of breast cancer its occurrence in the opposite breast is most important. Such an incidence has been estimated to be as high as 7.5 per cent[19] in some series. The patient who has had one breast involved by cancer should be viewed with especial suspicion on finding a nodule in the remaining breast. More will be said on this subject below (*see* p. 83).

With education of the lay public at such a peak, the classical picture of a large, hard, firm tumor which causes overlying skin and nipple retraction is not frequent. The diagnosis of such a tumor should be obvious to all doctors, and it presents no problem. It is the small tumor that gives few characteristic signs and which is diagnosed in the laboratory after its removal that is worthy of emphasis. Tumors under 2 cm. in size, and without axillary node metastasis, are problems in diagnosis and demand early removal and microscopic examination. When the diagnosis is microscopically confirmed specific therapy may be outlined.

Operability

There are many contraindications to performing a radical mastectomy. Some of these are obvious, a few more subtle. When confronted with a debatable problem which may or may not be best treated surgically, one is often reminded of the statement of Adair:[3] "Well, doctor, what better treatment have we to offer?" There are, of course, other ways of treating cancer of the breast, and

well meaning surgeons, by injudicious choice may possibly enhance the growth and spread of breast cancer To clarify the contraindications it is best to classify them into two groups. The "obvious" and the "questionably obvious"

The "obvious" group, as may be imagined, is simplest Patients with the following fall into this category

1. Metastases to lung, mediastinum or skeleton
2. Large, fixed, breast and chest wall cancers.
3. Large, ulcerated cancers
4. Intracutaneous nodules extending throughout the skin of the breast and associated with a deeper lying tumor.
5. Large tumors with extensive skin edema
6. Fixed axillary lymph nodes, with or without arm edema, or, unremitting arm edema alone.
7. Supraclavicular lymph node metastases

There is little disagreement among surgeons on these points They are obvious because they deal with the mechanical features of breast cancer Surgical resection should not be performed when the cancer and its metastases cannot be cleanly circumvented A large cancer, though, if not fixed, and with a free margin underneath, is not necessarily inoperable, but one should not underestimate the infiltrative nature of these tumors Surgical intrusion into the field may only disseminate the disease further.

The "questionably obvious" group is more physiological, and pertains to the finer relationships between cancer and patient. One cannot always afford to be dogmatic in this group because individual circumstances often alter one's opinion Patients showing the following fall into this group.

1. Pregnancy and lactation
2. Inflammatory carcinoma of the breast
3. Relentless skeletal pain, chiefly back, without x-ray evidence of metastases
4. Advanced age and debility

The basic factor in this group is a feeling on the part of the surgeon that metastases have already become widespread despite clinical evidence to the contrary Although this is most likely the case, it is wiser in these patients to consider each on an individual basis For example, opinions are divided[10,14,30] whether pregnancy contraindicates radical mastectomy, especially in the early trimester If performed then, one may also consider therapeutic abortion, although this too is debatable[30] During the later months of pregnancy there would appear to be more reason not to perform radical mastectomy as the exciting factor has had too long to act (*see* section on Postoperative Pregnancy p 82). The general feeling, however, is that pregnancy alone does not contraindicate radical mastectomy A statement of Adair[2] that 24 per cent of pregnant women with breast cancer on whom he operated survived five years is of interest The experiences of Haagensen[10] and Hendrick[11] do not support this

Inflammatory carcinoma, like pregnancy and lactation, are best individually

considered. Redness of half or less of the skin does not make the tumor inoperable, and unless it is associated with extensive infiltration skin edema and fixed axillary metastases surgery is not necessarily contraindicated. Oophorectomy and orchiectomy (in male breast cancer[34,35]) are recommended as prophylactic procedures when surgery is performed for these lesions

Relentless skeletal pain in the presence of a breast cancer is almost always due to metastases Roentgenological proof however may be lacking and in such instances the benefit of doubt understandably may be in favor of declaring the patient free of metastasis since to perform no operation would mean certain failure.

Concerning advanced age and debility one must employ careful clinical intuition In dealing with cancer it is best to consider age a physiological not a chronological matter As so often happens when one compromises with the treatment of cancer because of age the patient outlives all expectations, and the surgeon is confronted with a new problem far worse than the original one

Despite the points brought out in this discussion patients in the "questionably obvious" group have a universally high mortality from their disease However special consideration should be given them because of the complex and intangible nature of their problem, and the uncertainty of breast cancer in the individual patient.

Lymphatic Drainage of the Breast

The one, single most important prognostic sign of breast cancer is the number of involved lymph nodes found in the axilla There are nevertheless two chief lymphatic channels by which breast cancer disseminates the axillary and the internal mammary These are diagrammatically represented in Figure 8 With inner quadrant cancers about 70 per cent will metastasize first to the internal mammary chain, and between 20 to 30 per cent of outer quadrant cancers will do likewise after they have reached the axillary and apical axillary nodes Cancers in the subareolar or central portion of the breast will also metastasize to the internal mammary nodes in a high percentage of cases The supraclavicular nodes are usually not involved until both the apical axillary and internal mammary groups have become involved first.[9,12,13] Normal axillary lymph nodes are relatively large, 0.5 to 1.5 cm the apical axillary nodes smaller internal mammary nodes are very small, 0.2 to 0.5 cm normally and at times not much larger when involved by metastasis Further discussion of the lymphatics of the breast is to be found in the chapter on Radiotherapy (p 106) and Extended Radical Mastectomy (p 94)

Surgical procedures for cancer have as their basic tenet the removal of primary tumor lymphatic pathways, and lymph nodes in continuity It is this factor which makes the original Halsted[11] operation so effective when the disease is limited to the breast and axillary nodes If dissection of the internal mammary chain

is as effective the survival rate of breast cancer should appreciably increase This will be discussed further below

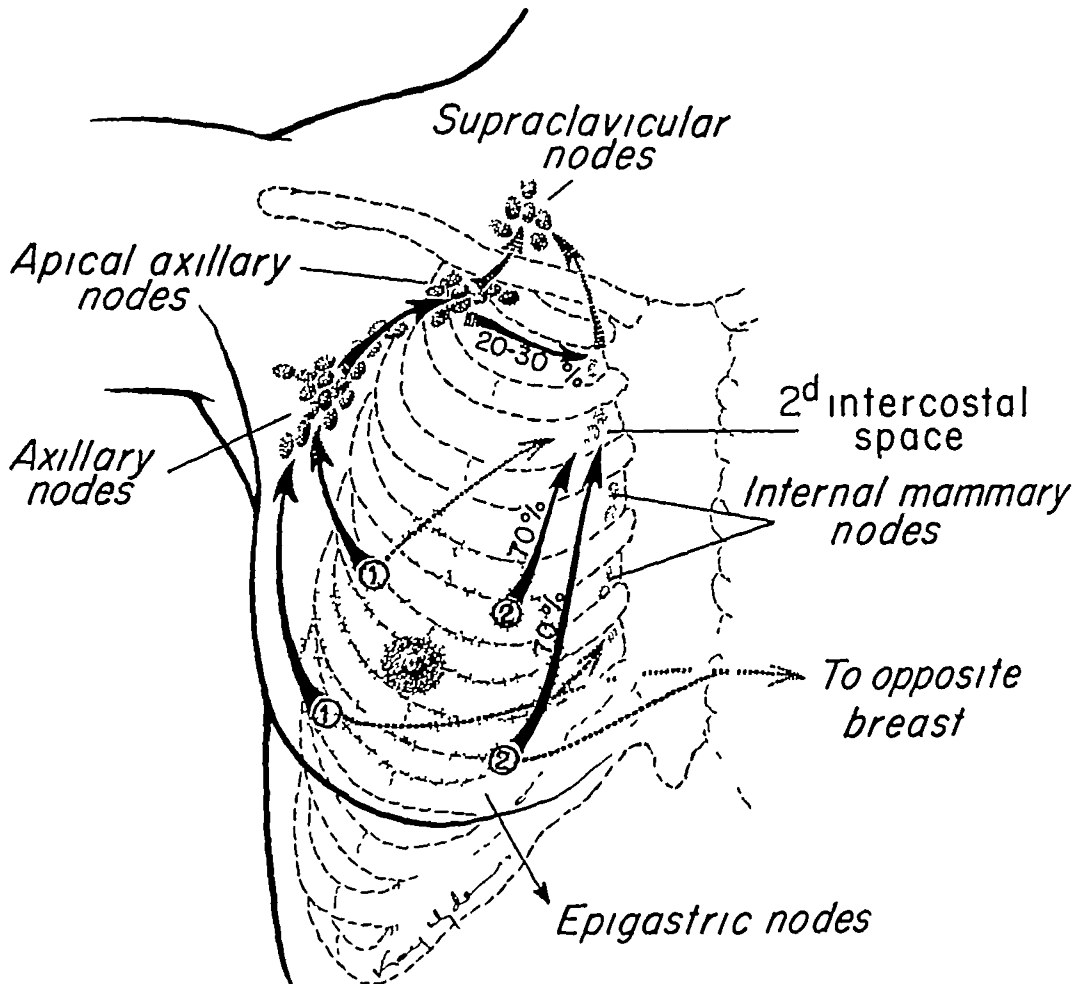


FIG 8 —Diagram of the chief pathways of lymphatic spread of breast cancer The heavy arrows show the more common routes, the broken arrows the infrequent routes.

Choice of Operation

The Halsted[11] or Willy Meyer[23] type of operation is advocated for the treatment of almost all operable breast cancers There are circumstances, however, where one may desire to change this rule By increasing the standard radical mastectomy to include the internal mammary chain of nodes it is hoped that this second major pathway of lymph borne metastases may be removed with resultant increase in survival rates To determine the nature of these nodes is of valuable prognostic importance also Routine biopsy of the internal mammary lymph nodes is practiced by R S Handley[12] at the completion of the radical mastectomy, and Haagenson[9] has suggested that this be performed before the radical mastectomy With tumors situated in the inner quadrants of the breast this may be a valuable procedure If the removed nodes are positive on examination, an

internal mammary dissection might be indicated. On the other hand, if, as has been suggested by Haagensen,[9] a supraclavicular node biopsy is also performed, and the nodes proved to be positive for metastasis, this would naturally contraindicate surgery. In doubtful cases, therefore, one may consider biopsy of axillary, internal mammary, and supraclavicular nodes, but this is not practiced routinely and certainly these procedures in themselves are not infallible or simple.

Whether dissection of the internal mammary chain is worthwhile remains to be seen. It undoubtedly is a logical form of treatment. For years it has been known that carcinoma of the breast may travel toward the mediastinum while the surgeon was directing his attention to the axilla. Nevertheless, one cannot yet be sure, because of insufficient time interval and study, that mediastinal dissection effectively removes the nodes and pathways as it does in the axilla. One has the uneasy feeling that to remove a segment of costal margin from the sixth to the first rib is a random and possibly ineffective procedure because of the multiplicity of lymphatic pathways in this area.[12,13] Radical mastectomy of the conventional type usually permits the removal of most but not all of the lymphatic pathways. It probably is sufficiently effective so that we shall not gain perceptibly by dissecting the internal mammary chain. The question remains whether the five and ten year survival rate following Urban's[18] procedure will differ appreciably from those for the standard procedure (*see* section on Results of Surgery, p. 88). Some breast cancers are a ravaging menace and are "inoperable" and incurable from their inception. These tumors make up the vast majority of our failures, failures which could not be prevented by mediastinal dissection (*see* chapter on Extended Radical Mastectomy, p. 94). At the present time, therefore, when confronted with a patient who has an operable breast cancer and on physical and roentgenological examination shows no evidence of metastases which contraindicate surgery, the author proceeds with a radical mastectomy of the conventional type without preoperative biopsies. In another section of this book (*see* chapter on Radiotherapy, p. 110) there is a radiological method of treating the internal mammary nodes which represents a rational and practical means of managing this aspect of breast cancer without surgery.

There are existing circumstances also which may compel one to do less than a standard radical mastectomy for operable breast cancer. As a general rule, breast cancer in the aged, seventy five and over, is slow growing and slow to metastasize. Simple mastectomy is worth considering in these patients when expected longevity is short and physical condition poor. It is easy, while performing a simple mastectomy, to remove many of the lymph nodes from the lower axilla. If they contain metastases, irradiation therapy to the axilla could be given and may serve to delay further dissemination for many months, even until death from other causes takes place. The method of McWhirter[26] simple mastectomy and axillary irradiation, is fully discussed in the chapter on Radiotherapy (p. 113). This method, too, represents a deviation from radical mastectomy and is to be considered in selected cases.

The procedure of simple mastectomy alone is not generally recommended In the average operable case of breast cancer it is inadequate, and for the so-called benign or "precancerous" lesions it is unnecessary Nevertheless, it is applicable in special instances, as above mentioned, and it is successfully employed as a palliative procedure[6] to remove foul, ulcerative, fungating tumors, to remove excessively large and pendulous breasts because of non-ulcerative tumors, and possibly as a prophylactic procedure following cancer in the opposite breast More will be said on this point later (*see* page 83)

SURGICAL TECHNIQUES OF SIMPLE, MODIFIED AND RADICAL MASTECTOMY

Incisions The recommended incisions for surgical removal of the breast are outlined in Plates 25*a* and *b* 26 27 and 28 When a simple mastectomy is to be performed incisions as diagramed in Plates 25*a* and *b* are preferred. These incisions, along with the undermined area totally encompass all of the breast tissue They differ from the radical operation only in the length and width of the skin ellipse Undermining and skin flap formation are considered essential in simple breast removal

Plates 26 and 27 show the incisions recommended for a modified radical and a radical mastectomy The upper end may start at the summit of the shoulder (Plate 26) or curve beneath the arm across the axilla (Plate 27) The scar is not so unsightly if this latter method is used, but axillary exposure is slightly more difficult

In patients with inner quadrant cancers incisions such as shown in Plate 28 are recommended. The medial portion is curved sharply to circumvent the cancer This makes it necessary to bring the lateral portion closer to the midline of the breast Such incisions are used when internal mammary node dissection is contemplated

There should be a comfortable, wide margin between tumor and incision. If there is skin dimpling ten or more centimeters on each side is not unreasonable Under no circumstances should one narrow the skin ellipse because of a desire to close the wound primarily without skin grafting All surgeons must be ready to perform a skin graft to obtain adequate closure if the wound edges do not approximate without tension

These incisions are only recommended Transverse incisions, upright "T" type and inverted "T" types are also frequently used with good healing The essential criteria of a good incision for breast amputation require that deep undermining of the skin flaps may be easily performed, and the axilla widely exposed Many incisions fulfill these criteria The surgeon will find it necessary to change the type of incision to fit the individual patient.

Skin Flaps and Undermining Following the incisions towels are applied to the skin margins and secured with towel clips (Plate 29) The biopsy site is similarly covered (Plate 29) The lateral flap is developed first (Plate 29) using fine dissection technique just beneath the skin This forms a truly thin skin flap which is dissected to the edge of the latissimus dorsi muscle In the simple mastectomy the flaps are not undermined as deeply as in the modified radical or radical operation.

The medial skin flap is made next (Plate 30) carrying the dissection down to the underlying pectoralis major muscle Superiorly the dissection reaches the

5

PLATE 25

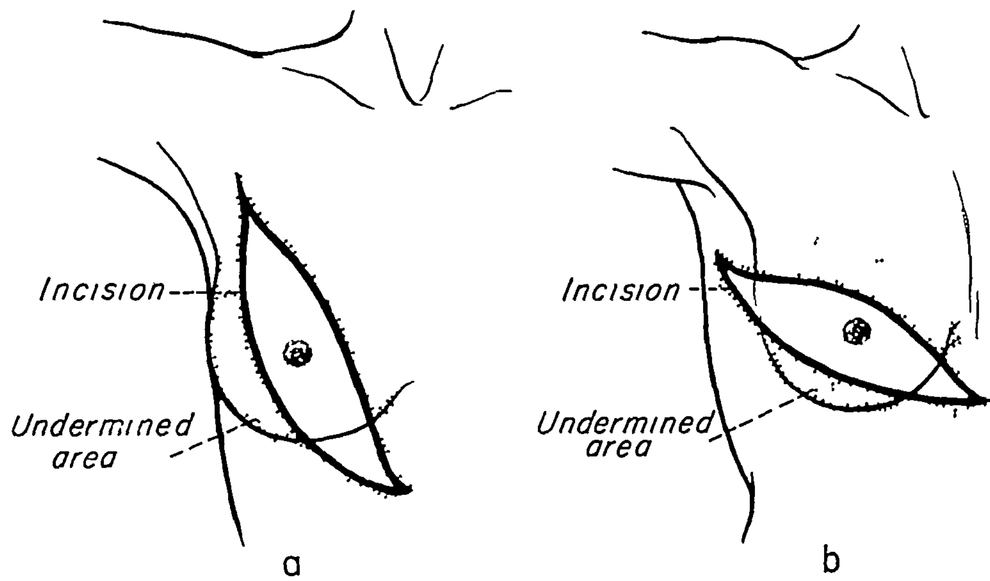


PLATE 26

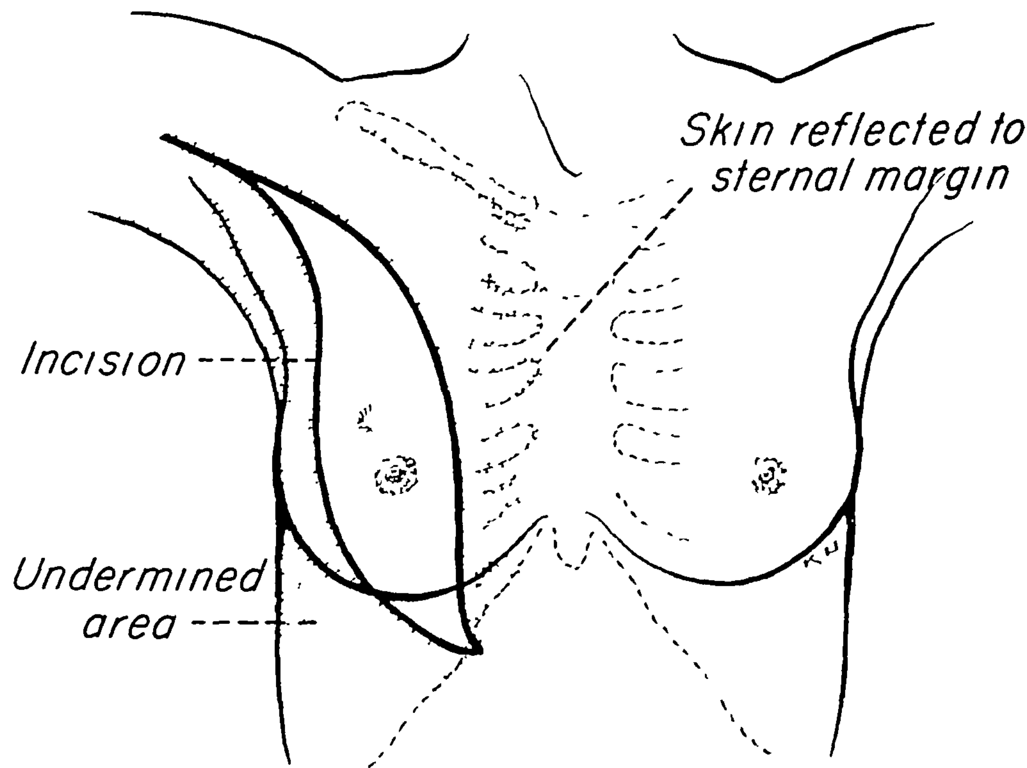


PLATE 27

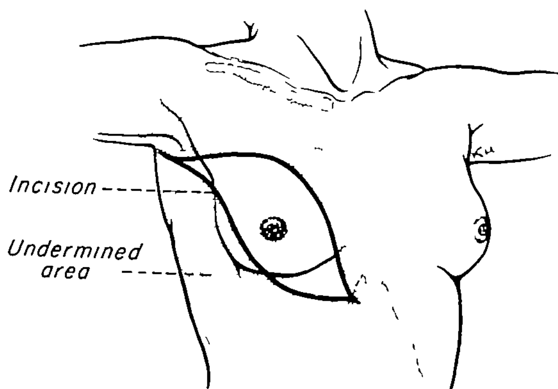


PLATE 28

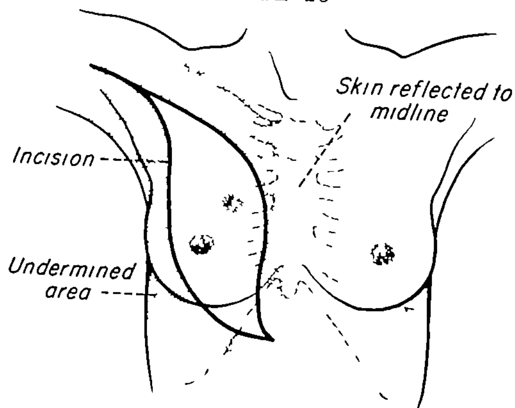


PLATE 29

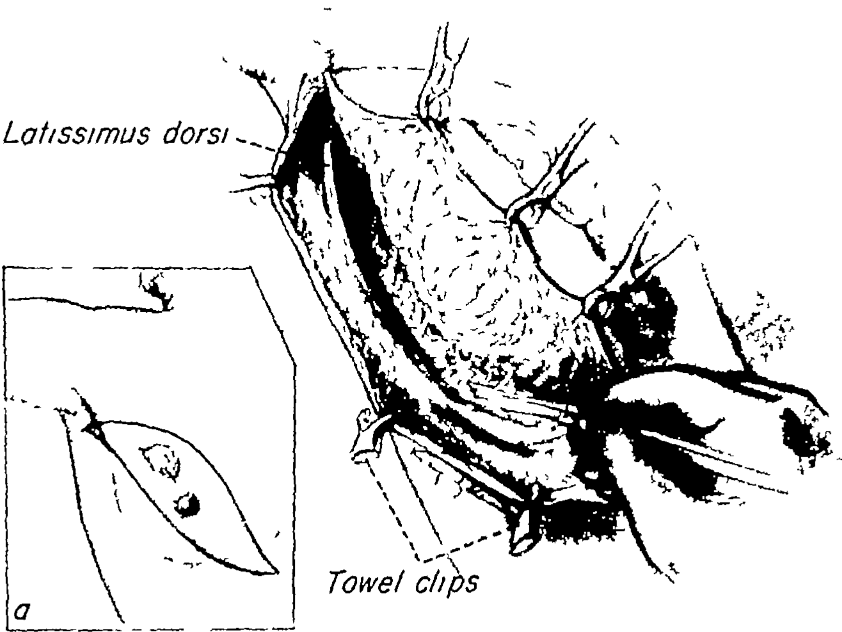
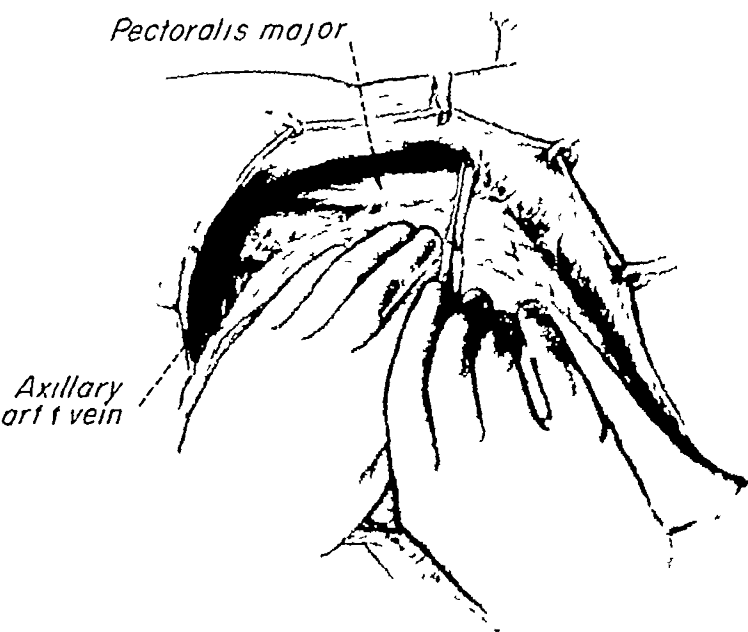


PLATE 30



clavicular portion of this muscle medially to the sternal margin (Plate 30) Upward traction on the towel clips by an assistant will facilitate elevation of the medial flap

Simple Mastectomy

With lateral and medial flaps developed the entire breast mass down to the underlying musculature is now freed Starting superiorly the breast mass is dissected off the underlying pectoralis major muscle (Plate 31) without disturbing the axillary contents The thin fascial layer on top of the muscle is usually removed with the breast. Soft rubber drains are placed at the lower angle of the incision and through a stab wound near the axillary portion of the lateral flap (Plate 39) The wound is closed with fine silk sutures

Modified Radical Mastectomy

Lateral and medial skin flaps are formed as described (Plates 29 and 30) dissecting more deeply and widely than when performing a simple mastectomy The breast is partly dissected off the underlying pectoralis major muscle, as far as the axillary edge so that the underlying axillary structures and costocoracoid membrane is exposed (Plate 31) With large retractors first the pectoralis major and then the pectoralis minor muscle, is retracted medially (Plate 32) exposing the axilla It is thoroughly dissected (Plate 32, also 35A 36 37 and 38) sweeping the axillary contents downward to meet the partially removed breast lying on the pectoralis major muscle The breast and axillary contents are removed together from the underlying musculature. The wound is closed and drained (Plate 39) A stab wound drains the axillary space

Radical Mastectomy

Wide and deep undermining with development of thin skin flaps is performed (Plates 25 through 30) The upper angle of the wound is retracted sharply exposing the insertion of the pectoralis major muscle on the humerus It is divided at its insertion (Plate 33) and separated from the clavicle and its sternal attachments (Plate 33) It is then partially dissected downward and laterally off the chest wall (Plate 34) The pectoralis minor muscle and axilla are exposed (Plate 34) The minor muscle is divided at its insertion on the coracoid process (Plate 35) and reflected downward The axillary apex is exposed and sharp dissection of the axilla is begun. (Plate 35A)

PLATE 31

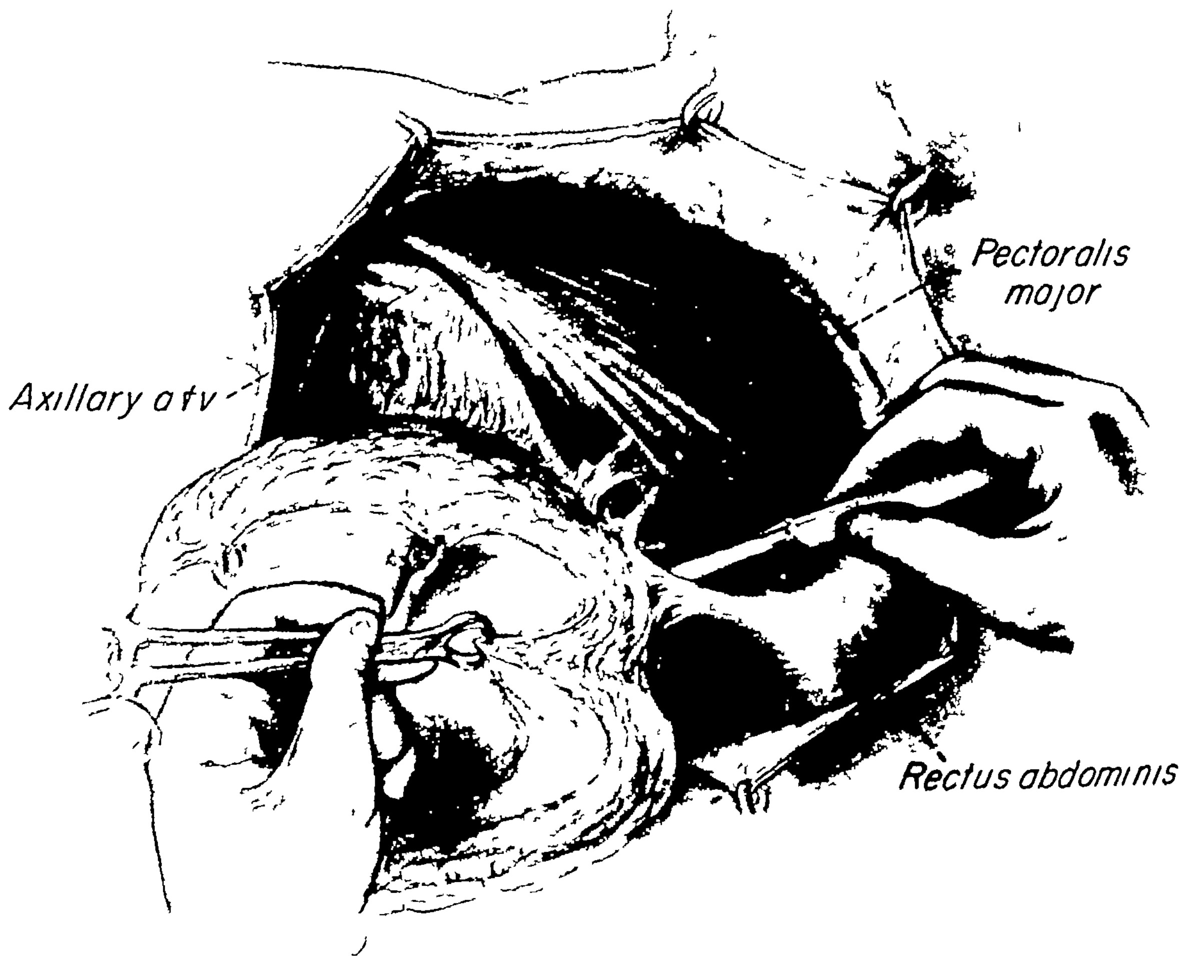


PLATE 32

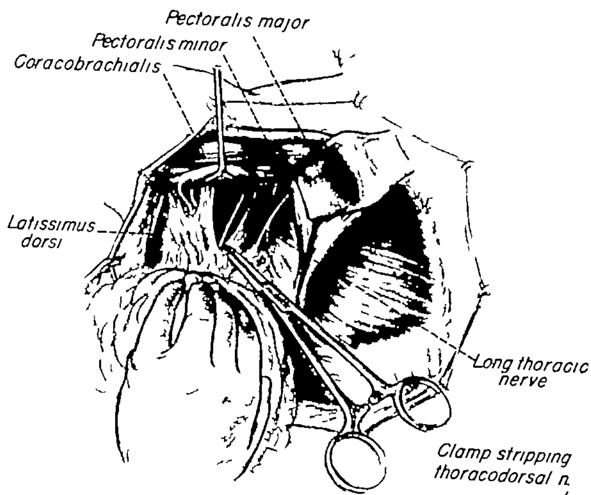

Pectoralis major
Pectoralis minor
Coracobrachialis
Latissimus dorsi
Long thoracic nerve
Clamp stripping thoracodorsal n.

PLATE 33

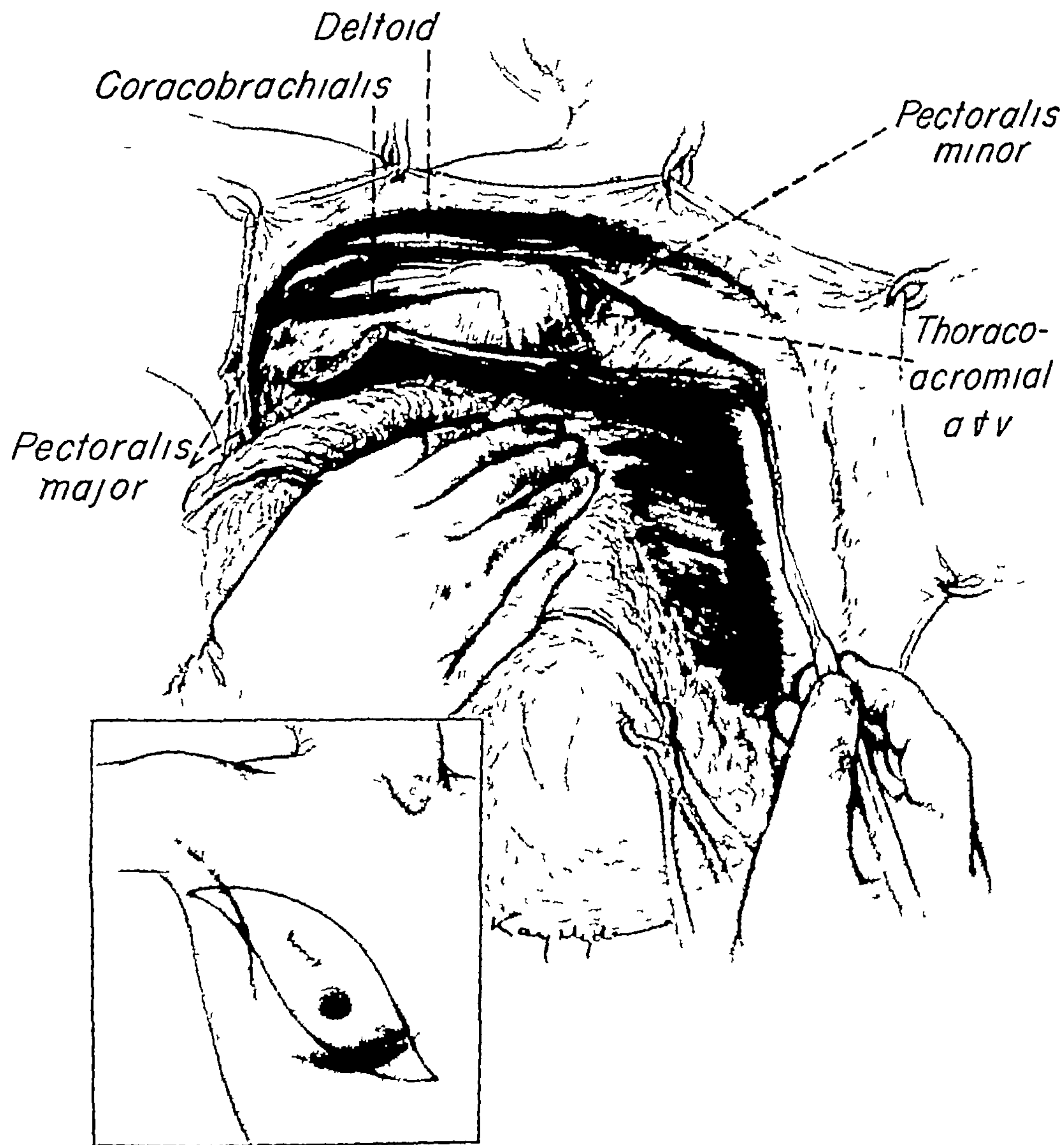

Deltoid
Coracobrachialis
Pectoralis minor
Thoraco-acromial a & v
Pectoralis major

PLATE 34

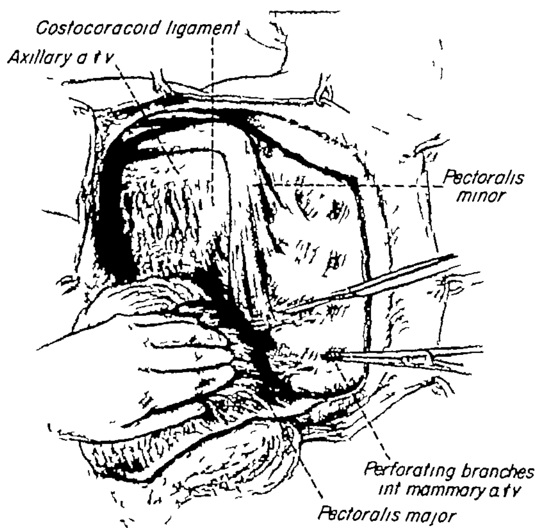
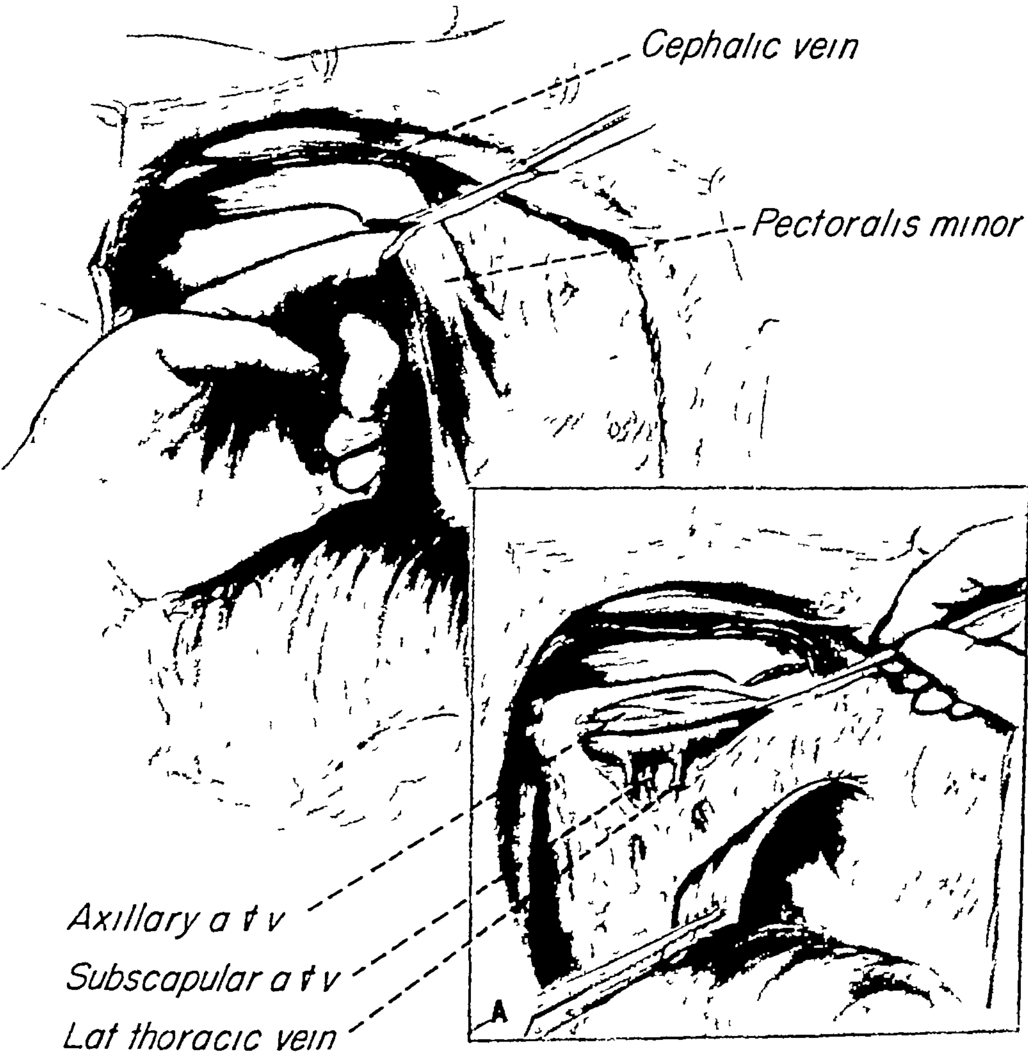

Costocoracoid ligament
Axillary a & v
Pectoralis minor
Perforating branches int mammary a & v
Pectoralis major

PLATE 35


Cephalic vein
Pectoralis minor
Axillary a & v
Subscapular a & v
Lat thoracic vein
A

The brachial plexus and great vessels are cleared (Plate 35A) The long thoracic nerve is identified, stripped and preserved (Plate 36) The costo-humeral bundle is swept downward, usually with a clamp (Plate 36) exposing and clearing the subscapularis muscle and a margin of the anterior serratus (Plate 37) The thoracodorsal nerve is identified and preserved, the thoraco-dorsal vessels divided, the axillary contents dissected downward clearing further the subscapularis muscle (Plate 37)

The pectoralis minor muscle is dissected off the chest wall to meet the partially reflected pectoralis major (Plate 38) The axillary contents are dissected further downward and meet the mass of freed pectoral muscles and breast (Plate 38) The entire specimen is dissected off the underlying anterior serratus muscle and chest wall. The wound is closed (Plate 39) A soft rubber drain placed in the axillary space through a stab wound and another drain placed at the lower angle of the incision provide adequate drainage

PLATE 36

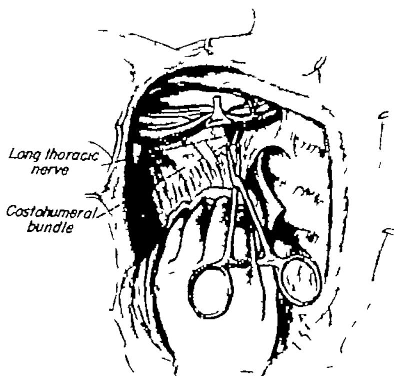


PLATE 37

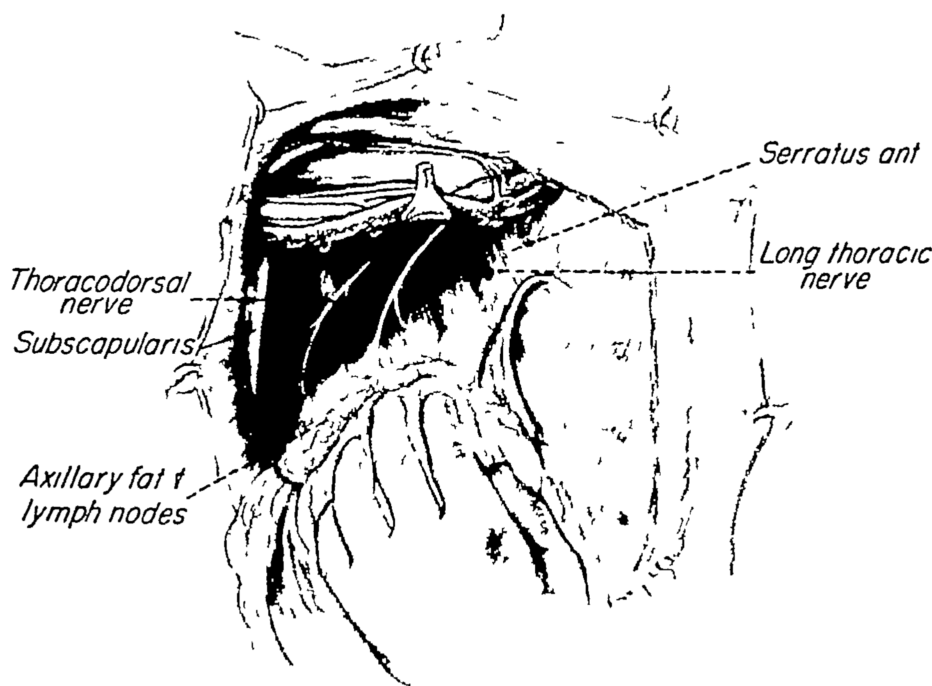

Serratus ant
Long thoracic nerve
Thoracodorsal nerve
Subscapularis
Axillary fat & lymph nodes

PLATE 38

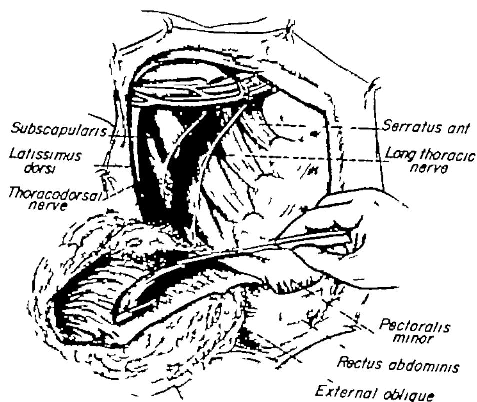
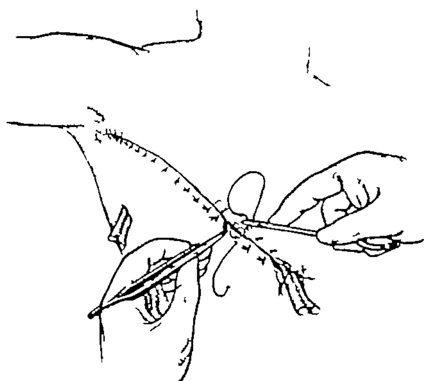


PLATE 39



Postoperative Care and Complications

Postoperative care and complications following radical breast surgery are best divided into immediate and latent classifications. The latter group includes lymphedema and lymphangiosarcoma of the arm, future pregnancies, management of the opposite breast, and the problem of recurrences. These will be discussed individually later. In the immediate group are items such as, control of hemorrhage, avoidance of infection, proper wound drainage, lessening of anesthesia morbidity, motion of the arm, psychic trauma and proper dressings. All of these are easy to control in the smaller, biopsy procedures. However, there may be difficulty following the radical and extended radical operations.

Blood loss at operation must be replaced by transfusions. Despite meticulous hemostasis during surgery there is a prolonged, slow oozing following the radical operation so that further blood loss occurs after the patient returns to her room. Shock may occur and its onset will be insidious. Close observation, therefore, is necessary during the immediate recovery period. For this reason it is preferable to bind the wound (chest wall) tightly with a heavily padded, bolster type dressing, wrapped around the patient with 6 inch bias stockingette (Fig. 9). This



FIG. 9 — Diagram showing large wrap around dressing with 6" stockingette. Note free arm.

controls oozing better than applying suction catheters under the skin The bolster dressing also enhances healing of thin skin flaps It is applied over these as one does with free skin grafts, pressing the flaps against the underlying chest wall. This large dressing is not disturbed for four to five days at which time it is removed, the drains shortened, and a new one re applied After the fourth to fifth day new dressings are applied as needed, depending on the amount of serous collection beneath the flaps This may be prolonged and considerable in obese patients, and every effort is made to drain it off as it collects The original drains are removed in a week, aspiration of serum through a large gauge needle and syringe is carried out thereafter A dressing such as this is kept on until all serous collection beneath the flaps has ceased.

Proper attention to sterile techniques, the use of antibiotics not routinely but as indicated, and adequate drainage will keep wound infections to a minimum. Early ambulation is practiced in all cases

Motion of the arm is started immediately Although the dressing is large and bulky the arm is kept free, elevated on one or two pillows and active and passive motion instituted the day of surgery Stretching and reaching exercises are given regularly throughout the entire hospital stay

Following the radical procedure there is, of course, much psychic trauma which in some cases can be marked. However in no instance has this resulted in any thing more than a transient depression By the time the patients leave the hospital, usually within a week, most will have adjusted well. With encourage ment, and after meeting other patients with similar difficulties, the problem seems to resolve itself A prosthetic appliance is used as soon as healing is complete.

Postoperative X Ray Therapy

Until the reports of McWhirter[38] there had been waning enthusiasm[10] for the use of postoperative *x* ray therapy Following the radical operation it had been customary in some clinics to treat the axilla, the supraclavicular area, and the chest wall with varying amounts of radiation on the supposition that any loose or remaining cancer cells would be destroyed and the results enhanced. This however was not the case Increased arm edema, and painfully sore areas of radiation dermatitis were all too frequently encountered as well as an under lying pulmonary fibrosis which caused intractable coughing Other surgeons used postoperative irradiation in selected cases, rather than as a routine procedure,[7,10] the decision to use irradiation depending on the degree of involvement of the axillary lymph nodes

With the advent of McWhirter's[38] method, namely simple mastectomy and axillary irradiation, and also due to the increased attention being given the internal mammary nodes, surgeons and radiologists have been forced to re-evaluate irradiation therapy Today when *x* ray treatment is given postoper atively it is concentrated primarily over the apical axillary internal mammary

and supraclavicular areas Areas which the surgeon cannot ordinarily reach with the standard operation There seems no purpose in directly irradiating an axilla which has been thoroughly dissected One relies on competent surgical technique to remove operable axillary metastases The chest wall is not irradiated either *X*-ray therapy to these areas is reserved solely for local, nodular recurrences

The following considerations are, therefore, made regarding postoperative x-ray therapy

1 Patients with cancers in the outer quadrants and who have no axillary lymph node metastases receive no postoperative irradiation
2 Patients with cancers in the inner quadrants, however, who have no axillary metastases do receive irradiation to the internal mammary and supraclavicular areas
3 Patients with cancers in the outer quadrants who have axillary metastases receive irradiation to the apical axillary, internal mammary and supraclavicular areas
4 Patients with cancers in the inner quadrants who have axillary metastases receive irradiation to the apical axillary, internal mammary and supraclavicular areas

This policy, which reflects numerous combined surgical opinions, as well as those of the Stanford University Hospital Department of Radiology (*see* chapter on Radiotherapy, p 109) has been practiced for the past five years. Whether the results with inner quadrant lesions will equal those treated by mediastinal dissection remains to be seen, but until more concrete evidence for dissecting the mediastinum is revealed this policy will continue (*see* chapters on Results of Surgery, p. 88 and Extended Radical Mastectomy, p. 94)

Adjunctive Procedures

It is quite apparent that surgery is not the sole answer to the present treatment of breast cancer Ancillary procedures which may increase survival times must be considered and used In 1896, Beatson[7] suggested the possible beneficial effect on breast cancer by removing the ovaries The subject is controversial, not because of the validity of his report, there is benefit derived from removing the ovaries. but because of the timing of the castration

A definition of terms is important Prophylactic removal of ovarian function is described as that which is done just before or immediately after mastectomy and before recurrences or metastases, other than axillary or internal mammary nodes, take place Therapeutic removal of ovarian function would be that performed after distant metastases and recurrences occur

The only phase of this subject which is not heavily debated is the method of removing ovarian function Surgical castration today is to be favored over x-ray, although the latter method has its advocates too[27] (*see* p 118) Convenience,

or the presence of skeletal metastases in the pelvic bones, may weigh in favor of irradiation This way one would include the ovaries in the *x* ray port covering the bony metastasis Nevertheless surgical castration is quicker more complete, and in the long run probably less painful.

To remove the ovaries in the premenopausal group is a matter for individual study The recent report of Treves[37] which is most complete, concludes with the statement that "in our mind it is still an undecided problem whether it would be advisable to reserve castration for therapeutic use when need arises, or whether in view of the prolongation of life as indicated by this study surgical castration should be used as a prophylactic procedure in all cases with very guarded prognosis. " In his series the survival rates of patients surgically castrated appear to be improved at the five-year level This improvement was especially notable among those patients with node involvement. Horsley[15] made an extensive study of the subject and also found that prophylactic castration did result in a higher five year survival figure especially in those patients with node involvement, than in the noncastrated group Contrariwise, there are others[23] who could find no essential difference in the two groups

Because of the lack of concrete evidence the independent surgeon is forced to individualize, and reserves prophylactic castration for the more serious or prognostically bad patients It is difficult to prove any noticeable difference between the two methods It might be best to withhold castration until it is therapeutically necessary especially since this is not a curative procedure and in itself is not a minor matter The response of bone metastases to castration alone is sometimes very gratifying Since there are only a limited number of "bullets" with which to treat disseminated breast cancer one is reluctant to "fire them off" quickly but rather conserve them, and use them slowly assessing the value of each and not using the next until the previous one has been tried. One s "strategic retreat" seems better covered in this manner With patients in the postmenopausal group vaginal smears are examined for evidence of estrogen activity If positive therapeutic oophorectomy would be performed when indicated by the presence of distant metastases (*see* chapter on Hormone Treatment, p 122)

Arm Lymphedema

Practically all patients who have undergone a radical mastectomy will develop some degree of swelling of the arm It appears to a lesser degree in patients under thirty five years of age. Meticulous dissection about vessels, many of which are clamped and ligated, removal of lymphatic channels scarring and fibrosis with diminished venous return, normally causes arm edema Such factors as postoperative infection, irradiation, or occult mediastinal metastases also tend to enhance the condition Obese patients seem to suffer more than thin ones In addition there is an idiopathic or unknown factor as well.[30] Lymphedema is much less frequent following radical mastectomy in men

The swollen arm is easily affected by a peculiar, red wave of cellulitis and infection, termed "erysipeloid," which responds readily to antibiotic therapy, as well as elevation and warm compresses The lymphedema, once pronounced, is progressive up to a point from which there are occasional partial remissions but never to normal

Treatment of the acutely inflamed phase is similar to that of any inflammation but there is no magic formula which will reduce the lymphedema once it is established Adequate, firm postoperative dressings, proper drainage, an infection free wound and early arm motion and exercise may tend to curtail or diminish this complication Suction catheters under the skin flaps postoperatively have made no difference

Muscle transplantation of the latissimus dorsi across the dissected axilla is recommended by some[14,18,20] but has not proved popular, and is of doubtful help It serves to obliterate the dead space across the dissected axilla, and possibly provide a tissue bridge for regenerating lymphatic channels It may be of use in cases of obesity where lymphedema seems to be almost the rule

In 1948 Stewart and Treves[32] reported on 6 patients with lymphangiosarcoma developing in the lymphedematous arm There have been other reports of this condition since then It is a very aggressive, virulent, malignant lesion which develops long after the mastectomy (average twelve years) It starts in the chronically obstructed lymphatics and presents as a "purplish-red, subdermal, slightly raised, macular or polypoid lesion on the skin of the arm near the anticubital fossa"[32] It is solitary initially, but gets confluent with other areas. The lesions become nodular, may ulcerate, heal and break down again, and eventually cover the entire extremity with spread onto the adjacent chest wall Radical amputation of the arm and shoulder girdle is the preferred method of therapy, if feasible Metastases are pulmonary

Postoperative Pregnancy

It has already been noted that cancer occurring during pregnancy or lactation does not in itself contraindicate a radical mastectomy. What then should be the advice of the physician to the young woman who contemplates marriage and family after her operation?

Little doubt exists that there is a stimulating effect of pregnancy on breast cancer The fact also exists that cancer cells may be dormant or "locked" in scar tissue for years and that a seemingly "cured" patient may actually harbor many foci of recurrent cancer The occasionally long dormant interval between operation and distant metastases, sometimes ten or more years afterward, tends to emphasize this point And since there is a 4 to 8 per cent chance of the opposite breast becoming cancerous an occult lesion here occurring during pregnancy would further lower the prognosis Also recommendations with reference to prophylactic castration would have to be discounted were pregnancy to be ignored

as a complicating factor More specifically the outlook of patients whose tumors were noticed during pregnancy but were allowed to deliver first, and then had their operation, is worse than those patients who had immediate surgery performed during their pregnancy [19] The same may be said of those patients developing cancer during the nursing period, that is, those who have immediate surgery without delay do better

The key point in this group of patients is the extent of the breast cancer at the time surgery is performed This, in general, is largely determined by the number of axillary lymph nodes (or internal mammary) involved. It has been shown[20] that patients with cancers limited to the breast will do well despite pregnancy or nursing However those with axillary node involvement do very poorly [20] If therefore, a patient has no axillary metastases (and one may say internal mammary node metastases on the basis of location of the lesion) at the time of her operation future pregnancies would not be contraindicated. On the other hand, patients who did have axillary node involvement would be wisest to avoid pregnancy in the future at least until an arbitrary interval of three to five years

The Opposite Breast

Each breast is subject to the same physiologic environment, and each breast is basically and inherently similar to the other Yet the realization that these two organs may in fact be considered as one is slow in gaining acceptance There is now however an increasing awareness[21] that the results of the surgical treatment of breast cancer may be enhanced by simple mastectomy of the remaining breast

The incidence of unsimultaneous primary cancer of the opposite breast is between 4 and 8 per cent.[21] At times, it is not easy to be certain whether one is dealing with a primary tumor or a metastasis Histologic study will not differentiate these lesions Naturally if each tumor is situated in the inner quadrants more doubt would exist as to the independent nature of each. On the other hand, in a patient with two outer quadrant cancers and no evidence of local or distant metastasis or recurrence one may fairly assume them to be unrelated. Involvement of the second breast by metastasis is uncommon without other evidence of metastasis or recurrence as well Given a patient, therefore with tumors occurring six or more months apart, and no other evidence of recurrent or metastatic cancer the probabilities are likely that one is dealing with an unsimultaneous second primary lesion

Simultaneous cancer in each breast is less frequent but should be considered The ideal management of a patient with simultaneous operable cancer in each breast is bilateral radical mastectomy staged five to ten days apart This may not be feasible in every instance and combinations such as radical and simple mastectomy with or without postoperative x ray therapy can be used

The same is to be said for the patient who develops another primary at a later

date, that is, a second radical mastectomy is ideal But, with a patient who has a diminished prognosis because of cancer in one breast, an impaired physiology, an increased morbidity, and the possibility that this second tumor could be a metastasis, the surgeon is justified in modifying the second procedure to a less radical operation in order to curtail postoperative discomfort and complications When, therefore, some doubt exists as to the curability of the patient, or the exact etiology of the second cancer, a simple mastectomy with axillary dissection would be preferable to radical mastectomy If the nodes are positive postoperative x-ray therapy is usually given One cannot help but feel that a patient who, for example, has had one breast removed because of cancer with axillary node metastases, and then develops another cancer in the opposite breast, probably cannot be cured unless the second cancer is limited to the breast itself Dissecting out the axillary nodes serves a therapeutic purpose, of course, but an additional advantage is in determining the extent of the cancer Morbidity is greatly reduced by following this more conservative approach and with little change in survival rates[22]

Because of the significant incidence of another cancer in the opposite breast prophylactic simple mastectomy has been advised either at the time of performing the radical operation[23] or after a waiting period of two years[8] The latter period is an arbitrary time limit to determine whether the patient has a reasonable chance of being cured of her cancer before undergoing further surgery No matter how logical this sounds it would seem that if prophylactic measures are to be undertaken the sooner they are performed the sooner they exert their effect, and that they might lose their effectiveness were one to delay the procedure beyond a few months after the radical operation In other instances prophylactic simple mastectomy of the opposite breast has been used selectively in those patients with strong family histories of cancer, in child bearing age groups where further children are desired, or in medially placed cancers

Unfortunately, despite its advantage to the average patient with breast cancer, prophylactic simple removal of the second breast is viewed with abhorrence by most patients and, thus far, has been seldom performed Nevertheless, with the patient who after frank discussion has no objections, the procedure should be performed and would prove worthwhile It should be discussed with all patients

Treatment of Recurrences

There are other chapters in this book which deal fully with the management and treatment of breast cancer recurrences (*see* chapters on Radiotherapy, p 116 *Hormones* p 122 *Adrenalectomy*, p 129 and Hypophysectomy, p 139), but there are several fundamental concepts which merit discussion at this time

Today patients with breast cancer are seen in an earlier stage of their disease and the local recurrence rate is far less than years ago, this despite the infrequency of grafting for wound closure Concurrently, improved techniques have also

reduced this complication Chest wall recurrences present as 2 to 5 mm., subcutaneous nodules along the scar If they are so situated that they can be excised this is ideal As a rule they do not lend themselves to clean excision and irradiation of the zone or area is usually better The same is to be said of axillary recurrences Surgical excision of these nodules may run the risk of further disseminating the disease and break down the scar barriers which tend to curtail its spread. At this time therefore, chest wall and direct axillary radiation play a major therapeutic role. The supraclavicular area would have to be included if node enlargement is found (*see* p 116)

It is to be emphasized that the best method of treating distant breast cancer metastases or local recurrences is with irradiation. This is especially the case when one is confronted with a localized skeletal or lymph node metastasis Relief of pain and regression in size of the tumor is usually rapid As the disease progresses one then employs more systemic measures. These in turn are oophorectomy oral or parenteral hormones, adrenalectomy and finally hypophysectomy Not until metastases or recurrences become generalized is oophorectomy performed in the premenopausal women and in those postmenopausal women who on vaginal smears show signs of estrogen activity Following this procedure it is worth waiting for several weeks to months to evaluate the effect rather than combine it with oral or parenteral use of hormones. Removal of the adrenals and the hypophysis is reserved for those patients with more advanced disease, and after oophorectomy and parenteral hormones have been given ample trial.

Cancer of the Male Breast

The considerations which have been discussed with reference to cancer of the female breast apply equally as well to the male The incidence of male breast cancer is under 1 per cent It is seen in a later age group than in women, yet the prognosis is felt to be more guarded. Similar histologic types of tumors occur in the male breast, including inflammatory carcinoma and Paget's disease of the nipple The breasts of male patients who are undergoing estrogen therapy for prostatic cancer should be closely watched for the development of cancer as a complication

Orchiectomy is recommended as a therapeutic measure for treating skeletal and soft tissue metastases and recurrences The response to this procedure[11] with male breast cancer seems to be more favorable than oophorectomy in female breast cancer There is no response to estrogens after the effect of orchiectomy has subsided Adrenalectomy and hypophysectomy may be worth consideration should the tumor give evidence of hormone dependency

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Chapter 7

RESULTS OF SURGERY AND EFFECT OF SPECIAL FACTORS ON RESULTS

NUMEROUS clinics throughout the world cite similar results in the treatment of breast cancer despite wide differences in case selection and methods of therapy. Some controversy has arisen as to whether the long accepted radical mastectomy is truly the most effective treatment[26,38] or whether all methods are equally effective.[30] The basic difficulty arises in comparing series which are not truly comparable. Variations in selection of patients for therapy and the known inaccuracy of a classification based on clinical staging are factors which greatly influence final results. Other significant factors include the age of the patient and the individual characteristics of the neoplasm, such as its histology, growth rate, size, duration, and location in the breast. No two reported series contain similar proportions of tumors of different histological degree and extent of malignancy. More uniformity in reporting is essential before any method of therapy can be accurately assessed.

The degree of malignancy based on histological grading often runs a close parallel with the extent of disease and period of survival. Grade I lesions are not as likely to metastasize as do Grade II or Grade III lesions.[12] Less than 10 per cent of Grade I carcinomas had axillary metastases while 88 per cent of Grade IV lesions were noted to have positive nodes.[16] Five-year survival dropped from 65 per cent in Grade I cancers to 16 per cent in Grade III cancers when axillary nodes were involved.[6] In Bloom's[6] series the histological grading did not vary significantly, either in separate areas of the tumor or in the nodal metastases. Certain histologic types, as medullary carcinoma with lymphoid infiltrate, have a relatively favorable prognosis when properly treated in spite of the large size primary frequently seen.[28,34]

There is a sharp increase in nodal metastases with larger size breast carcinomas.[10] Only 10 per cent of 28 patients whose tumor was less than 15 mm had positive axillary nodes.[11] The incidence of axillary metastases with tumors over 4 cm. was almost doubled that of tumors less than 2 cm.[35] Survival rates in cases with axillary node involvement showed a major decline from 54 to 22 per cent five-year salvage as the size of the primary lesion increased from under 2 to over 5 cm.[40]

The level of the axilla involved by tumor has considerable influence on prognosis. Invasion of the axillary lymphatic filter often begins in a progressive manner

at the base of the axilla and proceeds to the apex. Haagensen[15] believes the patient is categorically inoperable when the apex is involved, since it implies the supraclavicular nodes already contain deposits. By dividing the axillary contents at the time of surgery and labelling it with metal tags, the prognosis can be estimated by the level of nodal involvement. Adair[2] has cited 62 per cent five year salvage with the involvement of the base of the axilla, 45 per cent with the mid axilla, and 28 per cent with the apex.

Opinions differ as to whether the age of the patient at the onset of the lesion plays any part in prognosis. Some observers feel that results are poorer in the younger age groups.[20,30] Others believe that cancer occurring in women below the age of thirty, especially if the axillary nodes are not involved, has a more favorable outcome.[16,23] With tumors of equal extent, age probably exerts no significant influence.

It is generally believed that the longer the delay in treatment after onset of symptoms, the poorer is the prognosis.[20,25] Axillary node involvement was present in 74 per cent of patients who delayed twelve months before seeking treatment while only 55 per cent of patients who delayed one month had axillary metastases. Park and Lees[22] postulate that the time factor has not truly affected the cure rate, primarily because there are marked variations in growth rate between cancers of different degrees of malignancy. Lesions that increase rapidly in size in a limited amount of time often represent the more aggressive high grade tumors and the prognosis is always poorer. Evaluation of the biological behavior in terms of approximate rate of growth from the time of onset of symptoms may give some information as to ultimate prognosis.

The location of the primary lesion in the breast is thought to have a definite effect on cure rate. With a carcinoma occurring beneath the areola or in the medial quadrants of the breast in proximity to the internal mammary lymph nodes the prognosis was significantly lower.[16,44] Even where axillary nodes were negative, the medial quadrant lesions had a five-year survival of only 53 per cent in contrast to lateral quadrant lesions with a five year survival of 75 per cent.[30] Haagensen[12] found that cancers originating near the sternal border in the lower medial quadrant have the poorest prognosis and the highest recurrence rate. Others have not found significant difference in end results in relation to location of the primary tumor.[4,37]

A higher incidence of metastases to internal mammary nodes was present when the cancer began in the central or medial half of the breast.[8,12,13,44] By biopsy of internal mammary nodes at the time of radical mastectomy 29 per cent of all cases were found to have metastases to these nodes. When axillary nodes were positive, about two-thirds of all tumors located in the medial half of the breast had internal mammary node invasion.[14] The adequacy of the standard radical mastectomy in such instances is questionable and may explain the lower salvage rate. Prognosis cannot be accurately estimated with present methods of clinical staging based on axillary involvement alone. In a group of 75 patients

in whom biopsies were taken of internal mammary nodes at surgery, three-fourths of patients with only axillary node metastases were alive at the end of three years. Only one-third of those with both axillary and internal mammary node metastases were living at three years.[14]

Up to the present time radical mastectomy has yielded the highest cure rate for primary operable carcinoma of the breast. With this procedure approximately 50 to 55 per cent of patients live five years. When the axilla is involved, most clinics report five-year survival figures of only 35 to 40 per cent, but when the disease is confined to the breast, 70 to 80 per cent of patients are still living, free of recurrence, at five years (Table 1). At the end of ten years about 35 per

Table 1.—Five-year Survival Rate in Primary Operable Breast Cancer Treated by Radical Mastectomy

	Number of Cases	*Overall %*	*Breast Only Involved %*	*Breast Plus Axilla Involved %*
Memorial Center for Cancer and Allied Diseases[3]	3494	54.4	77.5	39.4
Lahey Clinic[24]	238	52.1	75.0	37.0
Mayo Clinic[17]	8224	52.1	78.1	33.1
University of Virginia[4]	324	54	74	37
Johns Hopkins Hospital[20]	220	44.1	64.1	31.7
Haagensen[12] (Personal Series)	356	56.7	78.8	38.8

cent of patients are still alive, and in fifteen years 25 per cent are still free of recurrence. If axillary nodes were negative at surgery, 49 per cent of these patients are still living at the end of fifteen years.[17] These results are often compared to Daland's[10] series of 100 untreated cases in which the average duration of life was forty months and the five-year survival rate was 22 per cent. The measurement of effectiveness of any form of therapy for breast lesions must improve these figures to be worth-while.

Some patients with apparently operable breast cancers are already beyond the scope of radical mastectomy by virtue of internal mammary and supraclavicular metastases. Attempts have been made to extend the procedure and thus better the salvage rate.[5,9,15,23,29,33,41,44,45] As yet, sufficient series of long-term survivors have not been reported. Wangensteen's[45] experience combining a radical mastectomy with an anterior mediastinal and supraclavicular dissection in one or two stages has been disappointing and yielded a five-year survival of only 17 per cent. Many of his cases were advanced at the time of surgery. Dahl-Iversen[9] has reported three-year survivals of 63 per cent without evidence of recurrence and five-year survival of 43 per cent by doing supraclavicular dissection and extrapleural removal of internal mammary nodes. Margottini[22] has shown a 14.7 per cent overall increase in five-year survival statistics utilizing an extra-

pleural internal mammary dissection and staged supraclavicular dissection The internal mammary vessels and nodes were removed en bloc along with the breast and axillary contents by Urban[48] in over 300 cases With 70 cases followed for over five years he has obtained a survival rate of 65 4 per cent, while 61 4 per cent of patients alive at five years have no evidence of recurrence Among these 43 clinically cured patients, 19 per cent of this group had positive internal mammary nodes at the time of surgery and 46.5 per cent had positive axillary nodes These figures are encouraging and seem to indicate there will be a definite increase in salvage especially where the lesion originates in the central or medial half of the breast.

Many other methods have been employed to improve results of radical mastectomy Preoperative radiation therapy (*see* p 108) only delays and complicates future surgery of the breast and has produced less satisfactory end results[20] In the postoperative period radiation is usually employed when the removed nodes are found to be involved Results were slightly improved after radiation was given for axillary nodes which were positive, but were inferior if no involvement was present.[17] In a group of 226 patients with positive axillary nodes 41 per cent of patients receiving postoperative radiation survived five years while only 32 per cent of those without radiation lived a similar period.[18] Marshall[21] employs this program for all patients after surgery although his results are similar to those where radical mastectomy only was done Others cite rates which show no improvement[7,20] with postoperative radiation therapy and are, in fact, inferior[6] This may be due partly to the fact that patients with more advanced lesions, or with lesions with unfavorable clinical features, often comprise the group referred for radiation therapy

Although present methods of treatment for breast cancer are not adequate, radical mastectomy still remains the standard treatment. Extension of radical surgery to include those areas not encompassed by the routine radical mastectomy probably will find its greatest indication with early subareolar or medial quadrant tumors Standardization of operative technique in performing a radical mastectomy is to be stressed, since even today an incomplete axillary dissection or inadequate removal of the primary tumor is seen Early detection of cancer before it is clinically obvious, careful selection of patients for surgery and prompt treatment are other factors which will better the results.

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Chapter 8

EXTENDED RADICAL MASTECTOMY

END-RESULTS with present methods of therapy for breast cancer indicate that approximately one-half of all cases die within five years. Considerable attention today is focused on the standard radical mastectomy, long accepted as the treatment of choice, but which fails to remove the internal mammary lymph nodes. Since these nodes are involved in about one-third of all cases,[6] radical mastectomy is destined to fail as a curative procedure in these instances. Patients with positive supraclavicular or internal mammary nodes are usually regarded as unsuitable for surgery because of poor results.[8] The failure of radiation to eliminate cancer in such locations has stimulated some surgeons to extend the classical radical mastectomy and encompass these areas. Whether the most effective method will be surgery, radiation, or a combination of the two has not yet been conclusively demonstrated.

The main lymphatic drainage of the breast is primarily to the axillary and internal mammary lymph nodes. From these depots secondary drainage passes into supraclavicular nodes at the base of the neck, and into the blood stream through the lymphatic ducts on the right and the thoracic duct on the left. There is a rich anastomatic lymphatic plexus occurring in the subareolar area which drains into both internal mammary and axillary nodes.

An English anatomist, Stibbe,[13] made the first complete study of the internal mammary lymphatics. An average of 8.5 nodes were found per subject. These were most commonly noted in the first, second, and third interspaces but were infrequent in the fourth or fifth interspaces.[9,13,15] When involved with cancer, nodes on the sternal side, medial to the internal mammary vessels, were positive in 82 per cent, while nodes lateral to the vessels were positive in 54 per cent.[15] The parasternal nodes are the last depot before generalized spread. Rarely are supraclavicular nodes involved if the axilla is negative and only the internal mammary nodes are positive.[3] The level of axilla involved, whether at the base or the apex, has no bearing on internal mammary involvement.[12]

Direction of lymphatic flow is greatly influenced by the position of the primary lesion in the breast and the presence of spread to the axilla. Handley[5] took biopsies of the internal mammary nodes at the time of surgery and found involvement in nearly one-third of all cases. When the axillary nodes were positive, the internal mammary nodes were involved in 74 per cent of lesions in the medial

half of the breast and 33 per cent of lesions in the lateral quadrants Even when the axilla was free of disease, the internal mammary nodes were positive in 8 per cent of cases The frequency of internal mammary node involvement has been expressed by others [3,14]

When preliminary biopsy reveals involvement of parasternal, supraclavicular or even highest axillary nodes, it is sometimes considered a contra indication to surgery [4] This attitude has been challenged, and final evaluation awaits the results of extended radical mastectomies or intelligently applied radiation therapy designed to encompass these areas

Margottini[9] in 1948 was first to attack the internal mammary nodes routinely In addition to a radical mastectomy he divides the costal cartilages of the upper four ribs and removes the internal mammary nodes and vessels along with the costal cartilages in an extrapleural manner Supraclavicular dissection is done at a later stage. Dahl Iversen[3] reported 376 extended radical mastectomies including a supraclavicular and parasternal dissection The costal cartilages were divided and the internal mammary vessels were dissected off extrapleurally along with nodes The latter was not in continuity Mortality rate was below 1 per cent In 20 per cent of cases internal mammary nodes were positive Wangensteen[17] and recently Noel[10] have combined a radical mastectomy with removal of the internal mammary chain an anterior mediastinal dissection and a supraclavicular dissection in one or two stages The overall mortality has been significant. Over one-half of cases were found to have involved nodes in parasternal or supraclavicular areas which could not have been removed by a conventional radical mastectomy

In an effort to extend conventional therapy to include the internal mammary chain without greatly increasing morbidity or mortality Urban[14] combined the radical mastectomy with an en bloc removal of the internal mammary nodes, vessels and chest wall from the first to the fifth interspaces The resulting defect was closed with fascia lata In 300 cases[16] mortality is less than 1 per cent and morbidity is only slightly increased. Hospitalization is not prolonged Positive internal mammary nodes were found in 35 6 per cent of these patients and axillary nodes in 47 6 per cent. Lesions in the medial half of the breast had involvement of internal mammary nodes in 60 per cent when the axilla was positive while with lateral quadrant lesions internal mammary nodes were involved in 40 per cent of cases [15] In 14 per cent, the internal mammary nodes were involved with tumor while axillary nodes were not.

Handley[7] now includes extrapleural removal of internal mammary nodes utilizing the pectoralis major for closure of the chest wall defect In 40 per cent of cases internal mammary nodes were positive Sugarbaker[18] found 52 per cent of medial quadrant and subareolar cancers to have positive internal mammary nodes. Ariel[1] described a more conservative en bloc resection of parasternal nodes with primary repair of the chest wall defect The ultimate in radical

surgery for breast cancer is described by Prudente[11] who has done 6 interscapulo-thoracic amputations for extensive disease.

It has been well documented that internal mammary nodes are involved in the majority of inner quadrant cancers and in subareolar carcinomas of the breast when the axilla is positive.[5,14] Since the axilla is involved in about 50 per cent of all cases, an operative procedure which attacks the axilla but which ignores the internal mammary nodes lacks some justification. Extension of surgery to encompass this area must, therefore, include complete removal of the breast and axillary contents as well as an en bloc resection of the internal mammary nodes, perforating veins and lymphatics. This must be accomplished without any undue increase in mortality and morbidity. Finally, this must add to the curability of the cancer. The Urban procedure appears to fulfill these demands. Although early results indicate that the cure rate will be increased, more time is needed before complete evaluation of results is available.

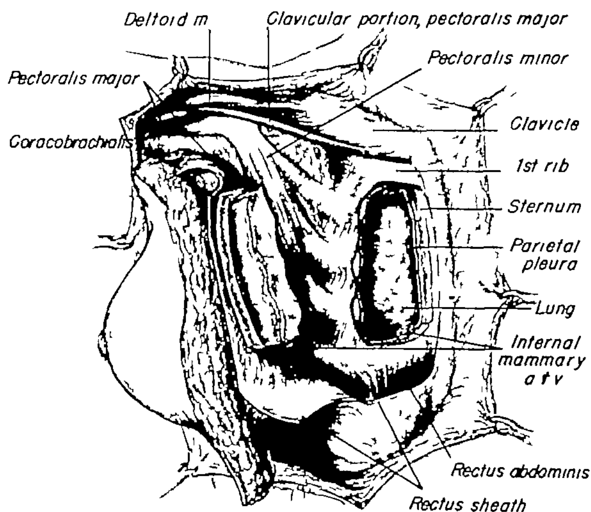
Surgical Technique

The patient is draped in a supine position with the arm extended at right angles from the body (Plate 1). The opposite thigh is prepared for removal of a fascia lata graft. A vertical incision is most commonly employed (Plate 28) extending from the clavicle to the subcostal margin encompassing the tumor by at least 10 cm. with upper quadrant lesions. A triangular type incision is made sometimes and subsequent closure is facilitated by suturing the skin in a "Y" shaped manner.

Thin skin flaps are elevated to the opposite border of the sternum medially, to the border of the latissimus dorsi laterally, superiorly to the clavicle and inferiorly to the subcostal margin. The upper portion of rectus abdominis fascia is included in the specimen. The pectoralis is then split between its costal and clavicular attachments, preserving the latter. The origin of the pectoralis is cleared off the fifth interspace just lateral to the sternal border. After carefully splitting the intercostal muscles of the first interspace, the internal mammary and intercostal vessels are identified and ligated. Palpation at the base of the neck is made to detect any node involvement. If present the procedure is discontinued as the disease would probably be generalized. If none is found the fifth interspace is entered and the internal mammary vessels again ligated just above the sixth rib (Plate 40).

After demarcating the line of resection on the sternum, a Liebsche sternal splitting knife is inserted in the first interspace, and the sternum split vertically between medial and lateral thirds down to the fifth interspace (Plate 10). The pectoralis major is undermined lateral to its attachment on the chest wall, thus exposing the costal cartilages of the second, third, fourth and fifth ribs. These cartilages and intercostal muscles are divided, and the flap of sternum and attached chondral segments of ribs with pectoralis major still attached is reflected back-

PLATE 40


Deltoid m
Clavicular portion, pectoralis major
Pectoralis minor
Pectoralis major
Clavicle
Coracobrachialis
1st rib
Sternum
Parietal pleura
Lung
Internal mammary a & v
Rectus abdominis
Rectus sheath

surgery for breast cancer is described by Prudente[11] v
thoracic amputations for extensive disease

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the border of the latissimus dorsi laterally, superiorly
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in the specimen. The pectoralis is then split betw
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fifth interspace just lateral to the sternal border
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vessels are identified and ligated Palpation at th
to detect any node involvement If present the
as the disease would probably be generalized If
space is entered and the internal mammary vessels
sixth rib (Plate 40)

After demarcating the line of resection on the
splitting knife is inserted in the first interspace, an
between medial and lateral thirds down to the fift
pectoralis major is undermined lateral to its attac
exposing the costal cartilages of the second, third, fo
tilages and intercostal muscles are divided, and the
chondral segments of ribs with pectoralis major s

PLATE 41

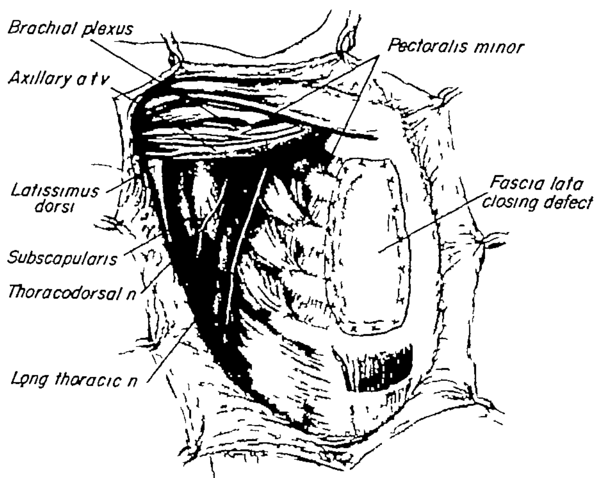

Brachial plexus
Axillary a & v
Latissimus dorsi
Subscapularis
Thoracodorsal n
Long thoracic n
Pectoralis minor
Fascia lata closing defect



FIG 11 —The skin edges are approximated and cotton bolsters used to prevent dead space and fluid collection beneath flaps The chest tube is connected to under water drainage

fifth postoperative day and again two days later The patient is discharged between the seventh to ninth day after surgery If a fascia lata graft was taken from the patient, Penrose drains in this area are removed on the third day, and firm pressure is maintained for several days following.

Arm exercises are begun soon after surgery Function is the same as following a conventional radical mastectomy There is no impairment of respiration as a result of chest wall resection, and the cosmetic appearance is essentially the same as that following a radical mastectomy

As yet, the final results pertaining to the efficacy of the extended procedure have not been completely defined (*see* chapter on Results of Surgery, p 88, also p 63) Whether the internal mammary nodes constitute a sufficient filtering bed for a time to prevent generalization of cancer cells is not known. Removing the internal mammary nodes does not attack supraclavicular spread However, when supraclavicular nodes are involved the disease is probably beyond surgical removal [3,17]

Radical mastectomy with chest wall resection will find its greatest application in early lesions that are centrally located or in the medial half of the breast Increase in cure rate is doubtful if there is massive involvement of either the

axilla or internal mammary chain of nodes Whether surgery or radiation, alone or in combination will be the most effective method to attack internal mammary nodes remains to be seen. Complimentary radiation therapy should be given to the base of the neck if nodes in the first interspace or apex of the axilla are positive It should never be used as a substitute for adequate surgery By careful selection of patients a 5 to 10 per cent increase in results may be possible with the extended procedure in patients who ordinarily would not survive with radical mastectomy alone.

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Chapter 9

RADIOTHERAPY OF BREAST CANCER

RADIOTHERAPY has become an integral part of the treatment of mammary carcinoma. At least half of the patients so afflicted will receive radiotherapy at some time in the course of their disease. One challenge that confronts the physician interested in treating breast carcinoma is to define clearly the role of radiation used either as a primary therapeutic weapon or conjointly with various surgical procedures. There are individual differences, but in general, the role of radiation in the treatment of breast carcinoma is supplementary to surgery.

PHYSICAL CONSIDERATIONS OF RADIATION RELEVANT TO BREAST CANCER

Ionizing radiation is the term collectively applied to certain rays and fast particles which are capable of producing ionization by displacing orbital electrons from atoms with which they collide. X-rays and gamma rays are of primary interest, since particulate radiations are infrequently used in treatment. The unit of measurement most commonly used for x-rays and gamma rays is the roentgen (r), defined in terms of the amount of ionization produced in air. Dosage has been generally expressed as "roentgens in air" but a more definitive and informative figure is the absorbed dose at the tissue or tumor, for which a new unit, the "rad," has recently been introduced and defined as an absorbed dose of 100 ergs per gram of tissue.

Low kilovolt x-rays (less than 140 kvp) exert their maximum biologic effect on the skin and immediately subcutaneous tissues because of their relatively long wave length. As the kilovoltage is increased there is an increasing penetrability, and thus, a greater relative amount of ionization reaches the tissues below the surface. At the present time 200 to 250 kilovolt x-rays are most commonly employed in deep x-ray therapy.

Supervoltage x-rays are produced at peak energies in the range of 1 to 6 million volts. Their major advantage lies in their ability to deliver a relatively large depth dose compared to the surface dose. At the higher energy ranges maximum ionization takes place below the surface, and thus the skin is spared (Fig. 12).

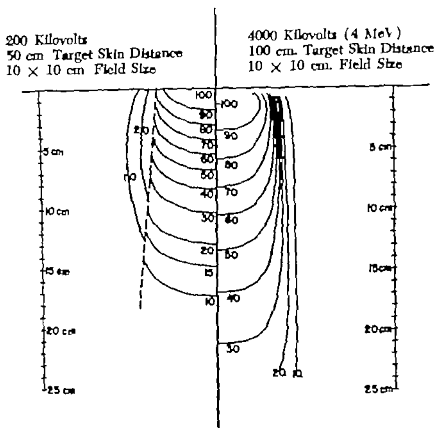


FIG. 12.—Comparison of isodose curves obtained with 200 kilovolt and 4000 kilovolt (4MeV) x rays.

Gamma rays emitted by radium and certain radioactive isotopes (Cobalt[60]) are being used more frequently now as teletherapy sources For practical purposes they can be considered as having essentially the same ionization charac teristics as supervoltage x rays

BIOLOGIC CONSIDERATIONS OF IRRADIATION OF BREAST CANCER

The exact physical and chemical mechanisms involved in producing radiation injury in cells and tissues are unknown. However on the basis of numerous investigations, ranging from irradiation of unicellular organisms to human malignancies, several modes of cellular damage have been described It has long been known that cells which divide are more likely to show evidence of radia tion damage than cells that are mature and incapable of further division. It is on the basis of this fundamental observation that radiotherapy has been applied to malignant neoplasms, since the mitotic rate of each growth tends to be greater than that of their surrounding normal tissues Radiation injury at the cellular level is manifested by (1) a failure of the cell to divide, with subsequent lysis

or giant cell formation and ultimate cell death, (2) abnormal mitotic cycle, manifested by delay in entering mitosis, prolongation of mitosis, particularly in prophase, chromosome aberrations with "stickiness," and multipolar, frequently nonviable divisions, (3) genetic damage manifested by delayed cell death or abnormal development after a varying number of mitotic divisions. The above observations are presumably due to an alteration in the desoxyribonucleic acid component of the nucleus of sufficient magnitude that the cell line cannot propagate.

Recently, interest has centered on the role of oxygen on the biologic effect of radiation. The present theory is that oxygen is necessary to convert short lived radicals to more efficient peroxides. Although further basic research into this reaction is needed, the clinical implications of the oxygen effect deserve comment. If a tumor has a poor blood supply, as is frequently the case in zones which are necrotic, the cellular oxygen level is insufficient to allow development of the maximum radiation reaction. This may in part explain the relative insensitivity to radiation of large solid or fungating tumors. It is suggested that if maximum oxygenation at the cellular level could be physiologically obtained, radiosensitivity would be enhanced with a corresponding increase in the radiocurability of the tumor.

At the tissue or organ level, radiation effects are observed as the cumulative injuries of the myriad of irradiated cells. This is manifested by altered physiology of the organ or organs involved. Of particular importance in radiation therapy of cancer is the alteration of the blood supply by the effect of irradiation on the endothelium of capillaries, small arterioles and venules. This effect secondarily impairs the growth potential of the tissue involved, probably by virtue of anoxia and an insufficient nutritional supply to meet the demands of the tissue. Alteration of the connective tissue stroma and blood vessels undoubtedly plays an important role in the final destruction or inactivation of irradiated tumors.

Fractionation, or the division of the total amount of radiation given over a specified period of time, is based on the clinical finding that normal tissues are capable of recovering from radiation injury when the dose is given in relatively small increments. In contrast to this, most malignant tumors are incapable of such rapid recovery from radiation injury, and thus a differential is developed. By careful exploitation of this differential rate of recovery, radiotherapists have been able to deliver cancericidal dosages into malignant tumors with a minimum of permanent radiation injury to the adjacent normal tissues. The optimum time dose relationship varies with the clinical problem, but an average cancericidal tumor dose is 5000 to 6000 r delivered in five to six weeks.

Ionizing radiations are capable of causing cellular changes in breast carcinoma, but the question that remains is whether irradiation can completely eradicate the carcinomatous tissue without irreparably damaging adjacent normal tissue. This problem has been studied by many investigators in an attempt to decide upon

an optimal time-dose relationship Of great importance in evaluating the results of irradiation of breast carcinoma is the knowledge that this disease is infinitely variable in its biologic growth characteristics The histology varies widely from patient to patient, and even at times within the primary tumor itself Bloom[7] correlated histologic grading with clinical staging and demonstrated that the five-year survival rate will vary within the clinical staging depending upon the grade of malignancy Taylor[32] and Watson[37] also found that the five-year survival rate was lower in patients who had breast carcinoma with a high grade of malignancy as determined by histology The role of the tumor stroma, hormonal influence, and normal tissue resistance must be assessed to fully appreciate the effect of irradiation on breast carcinoma

Lumb[21] carefully studied the effect of histology with 200 kilovolt *x* rays on 60 cases of breast carcinoma treated at Westminster Hospital, London The dosage administered ranged from 2000 to 4000 r given in twenty to forty days He found (1) acute cell dissolution (2) alteration of cell structure with nuclear pyknosis, vacuolization in the cytoplasm giant cells and subsequent calcification (3) connective tissue changes with obliteration of small blood vessels and replacement of tumor areas with strands of acellular material These changes were not present in all cases, and he found no remaining cancer cells in only 7 out of 60 cases 4 of which were among the 11 cases receiving the maximum dose of 3500 to 4000 r His conclusion was that a dosage of 3500 to 4000 r is the minimum effective tumor dose. He found that he could not rely on histologic criteria to determine which carcinoma would respond to a lower tumor dose

Lenz[18] reported that the mastectomy specimens in all 38 patients given a tumor dose of 4500 r in one month revealed microscopic persistence of cancer cells Williams[38] reported on 18 cases initially inoperable and given preoperative irradiation after biopsy Microscopic evidence of viable carcinoma was found in 17 of the 18 cases. The case in which no viable carcinoma was found was 1 of 4 treated with supervoltage (1 mev) *x* rays to a total tumor dose of 4500 r in thirty days The other 14 reported cases were treated with 250 kilovolt *x* rays to an estimated tumor dose of 3000 to 3200 r in twenty-eight days Surgery was performed on these patients from four weeks to eighteen months later Williams[38] also notes that 4 of 9 cases with positive axillary nodes preoperatively had persistence of the carcinoma in the nodes removed at operation Williams[38] cites 18 other advanced cases treated by Ross and Boyd with *x* rays at a half value layer of 1 to 1.5 mm Cu up to a tumor dose of 3000 to 3500 r in twenty-one days All of these cases showed microscopic evidence of viable carcinoma cells in the primary tumor after mastectomy In 13 cases in which axillary dissection was performed, positive nodes were found in 12 despite a tumor dose of 3000 to 3500 r

Baclesse[5] described in detail his method of preoperative roentgen therapy followed by a radical mastectomy Seventy seven cases were treated in this manner from 1935 to 1956 Dosages varied from 4500 to 9000 r in a period ranging from ten to sixteen weeks At no time was a severe skin reaction

allowed to develop, the maximum reaction noted was a dry desquamation Of the 77 cases, 9 were found to have no demonstrable carcinoma cells in the primary, but only 1 of the 9 cases with the primary "sterilized" had no viable cancer cells in the axillary nodes.

Irradiation as given by these investigators proved inadequate for complete eradication of breast carcinoma in the majority of patients However, viability is a difficult microscopic interpretation, particularly if the specimen is examined relatively soon after the irradiation Possibly irradiation induces in many breast carcinomas a period of dormancy, and therefore relative control without eradication

THE REGIONAL SPREAD OF BREAST CANCER

Halsted realzed that breast carcinoma metastasized not only to the axillary group of nodes, but also to the internal and supraclavicular chains Handley[13] rekindled interest in the problem of early spread to the internal mammary chain It was his discovery that the internal mammary nodes are involved 3 times as frequently with inner quadrant tumors as with outer quadrant tumors, that has stimulated surgeons to re-evaluate the classical Halsted radical mastectomy Handley[14] also pointed out the increase in internal mammary chain involvement when the axilla is involved regardless of primary site, though again inner quadrant tumors have a higher percentage when compared to outer quadrant tumors (Table 2)

Table 2 —Sites of Microscopic Metastases in Carcinoma of the Breast

Author	*Number of cases*	*All nodes free*	*Axillary nodes alone*	*Internal mammary nodes alone*	*Axillary and mammary nodes*
Handley (1950, 1956)	122	39	37	16	30
Wyatt (1955)	60	22	19	7	12
Dahl-Iversen (1951, 1954)	153	82	44	8	19
Margottini (1948)	110	41	44	2	23
Hutchinson (1949)	81	38	22	2	19

Dahl-Iversen[9] initiated several series of extended radical mastectomies for breast carcinoma with the aim of finding out how often the ordinary radical operation failed because of supraclavicular or internal mammary node metastastasis The sites of metastases in his fourth series are presented in Table 3 Wyatt[22], in a series of extended radical mastectomies, confirmed Handley's finding that the site of the primary and axillary node involvement are paramount factors in determining internal mammary node involvement Haagensen[10] also confirmed the greater likelihood of internal mammary node metastases when the primary

tumor is in the medial or central portions of the breast Hutchinson[17] and Margottini[22] were unable to confirm Handley's finding regarding an increased frequency of internal mammary node metastases with inner quadrant tumors but did find that approximately 20 per cent of patients with axillary node metastases did have involvement of the internal mammary nodes at the time of radical mastectomy

Table 3 —Sites of Microscopic Metastases and Primary Growth in 100 cases of Carcinoma of the Breast (Andreassen, Dahl Iversen and Sorensen, Courtesy of Lancet 1954)

	Site of primary growth	
Site of metastases	*Medial*	*Lateral*
Axillary only	4	21
Parasternal only	4	0
Axillary and parasternal	7	6
Axillary and supraclavicular	0	3
No metastases	22	33
Total	37	63

Supraclavicular metastases are found only in patients with axillary metastases The incidence of these nodal metastases is lower than that of internal mammary node metastases, presumably because they occur at a later stage. Dahl Iversen[9] found supraclavicular metastases in 7 to 33 per cent of cases with axillary involvement. This variation is apparently dependent upon differences in the clinical material available for his series

The size of the primary carcinoma and the incidence of axillary metastases have a positive correlation, and this is presumably true for internal mammary node metastases as well The critical diameter at which the majority of breast carcinomas will metastasize is unknown, but various observers believe it is between 2 and 4 cm Robbins[28] found axillary metastases in 39.5 per cent of cases with a primary less than 2 cm in diameter compared to 74 per cent when the primary was 4 cm. or over Haagensen[10] concurs that most large carcinomas have metastasized when the patient is first examined, and reports a 77 7 per cent incidence of axillary metastases when the primary is 7 cm or larger

From the foregoing review two conclusions can be drawn The site and size of the primary carcinoma in the breast determines the frequency and direction of metastatic spread to the regional lymph nodes As the degree of axillary node involvement increases metastatic disease will be found more frequently in the internal mammary and supraclavicular nodes

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TREATMENT OF BREAST CANCER WITH IRRADIATION

Preoperative Irradiation

Although several European centers have advocated this technique for many years, it is no longer routinely employed in the United States. Ash[3] presented the following points in favor of preoperative irradiation: (1) ability of irradiation to destroy cancer cells, (2) effectiveness of post-irradiation fibrosis in devitalizing the cancer cell, (3) higher tumor dose possible, (4) normal tissues become less receptive to implantation, (5) devitalized cells spread by operative trauma are innocuous, (6) regression of an inoperable lesion may make surgical treatment possible, and (7) there is no delay in initiating treatment. Ash[4] suggests that preoperative x-ray therapy should be given in all Stage III cases where: (1) the tumor is larger than 6 cm., (2) smaller than 6 cm. with axillary nodes, (3) small tumor in medial quadrants showing retraction and axillary nodes.

Berven[6] used preoperative radiotherapy in all operable cases, and attempted to deliver a tumor dose of 2000 r to the breast and 1500 r to the axilla in 10 days. This was followed in three weeks by a radical operation, and then by postoperative irradiation given as soon as the wound healed. Richards[27] gave a tumor dose of 3500 r to the breast and 1800 r to the axilla prior to radical mastectomy. As evidence of its efficacy he reported a five-year survival rate in 15 Stage II cases of 66 per cent and in 52 Stage III cases of 39 per cent.

Baclesse[7] reported on 77 cases given preoperative roentgen therapy. No Stage I cases were included in the series. He emphasizes that only a dry desquamation should be allowed to develop, and therefore takes up to ten weeks to deliver a 4000 r skin dose to lateral and medial tangential breast fields. The internal mammary chain is treated separately to a skin dose of 6000 r. The supraclavicular area is treated through a single triangular shaped field to a skin dose of 4000 r if no nodes are palpable or to 7000 r if large nodes are noted. The latter dose may require four months to deliver. With his technique Baclesse has noted a 44 per cent five-year clinical cure rate. The majority of those "cured" are in early Stage II class.

Haagensen[10] believes that clear-cut conclusions cannot be drawn from the available statistical data on the value of preoperative x-ray therapy. He presents the following arguments against preoperative irradiation: (1) a minimum tumor dose of 5000 r is necessary to arrest breast carcinoma and this cannot safely be delivered to the primary tumor and regional node areas in less than six weeks, (2) surgery cannot be safely carried out until "radiation reaction" has subsided, and thus, definitive treatment is delayed for at least four months.

Preoperative irradiation should not be discarded without a fair, soundly designed clinical trial utilizing the latest techniques of radiotherapy. Such techniques require the use of supervoltage irradiation to the chest wall, axilla

and supraclavicular area. A tumor dose of 4500 to 5000 r could be given in four to five weeks, without the intense skin reaction seen with 200 kilovolt *x* rays at this dose level Surgery could then be done six to eight weeks later with a minimal increase in surgical difficulties or complications

Postoperative Irradiation

Postoperative irradiation in breast cancer has wide appeal. It is based on the argument that radiotherapy destroys any cancer remaining after surgery and that possible avenues of spread, such as the supraclavicular fossa and the parasternal regions can be effectively sterilized *X* rays are generally used since the volume of tissue requiring irradiation cannot be conveniently irradiated with radium.

Patients receiving postoperative roentgen therapy fall into three broad groups those that had their carcinoma entirely removed by surgery and in whom, therefore, the therapy is unnecessary those with undetected distant metastases at the time of surgery in whom the therapy cannot help and finally those with spread limited to the supraclavicular and ipsilateral internal mammary nodes who might be expected to benefit from such therapy

Smithers[31] does not doubt that in cases with axillary node involvement postoperative irradiation improves the survival rates Smith[30] in a review of breast carcinoma seen at Pondville, Massachusetts Hospital noted that 85 per cent with positive axillary nodes received supplementary *x* ray therapy He suggests that it is the supplementary *x* ray therapy that accounts for a five-year survival rate of 41 per cent as compared to 22 per cent for those cases with positive axillary nodes but no irradiation In addition he found an increased survival in those patients with Grade III tumors (based on a scale of IV) and negative axillary nodes receiving *x* ray therapy postoperatively as compared with those with similar tumors negative axillary nodes and no *x* ray therapy

Haagensen[10] does not use postoperative *x* ray therapy routinely preferring to reserve it for those patients who are found to have extensive axillary involvement. As accuracy in the application of his strict criteria of operability[11, 12] has improved, relatively few patients are subjected to supplementary irradiation When it is given, a two portal technique, utilizing 2 mev *x* rays and covering only the supraclavicular fossa and parasternal regions is employed. He offers no figures as to relative survival rates and the irradiation is given in the hope that it may add to the patient s chance for cure

The value of postoperative irradiation is difficult to define in a clear-cut fashion because of the multiplicity of factors that govern its usage either on a routine or individualized basis It is in patients who are expected to do poorly with surgery alone that irradiation is advised, and thus survival rates may give an erroneous estimate of its value.

The policy currently adopted at Stanford University Hospitals is based on the

view that surgery, in properly selected cases, can effectively eradicate the disease in the breast and axilla, and therefore, routine postoperative x-ray therapy in all patients is unnecessary. In patients with (*a*) extensive axillary involvement, or (*b*) medial quadrant tumors, postoperative x-ray therapy is given to the apex of the axilla, supraclavicular fossa and first three interspaces of the ipsilateral parasternal area. For the supraclavicular field supervoltage at an energy level of 4 to 5 mev is used, whereas for the parasternal field we prefer to utilize 140 kilovolt x-rays in an attempt to spare the deeper mediastinal structures from needless irradiation. The parasternal field measures 6 × 9 cm and abuts the inferior margin of the supraclavicular field which has an average size of 10 × 12 cm (Fig 13).

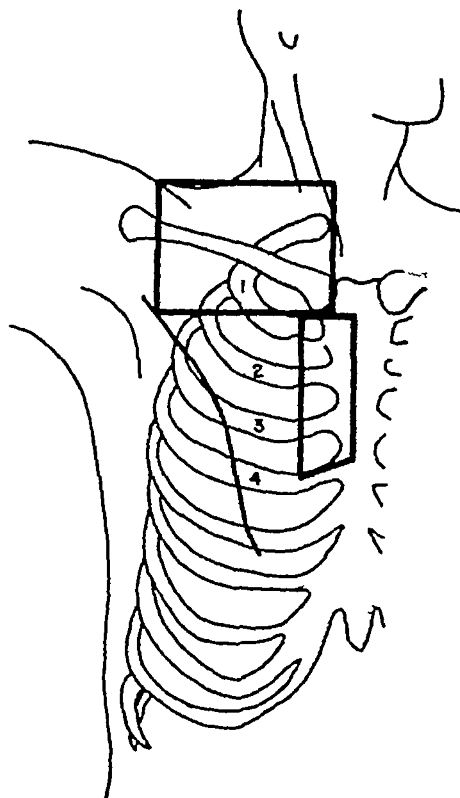


Fig 13.—Portals used for postoperative irradiation. Supervoltage x-rays are used for supraclavicular and axillary apex area. 140 kilovolt x-rays are used for upper parasternal region.

Only the first three interspaces on the ipsilateral side are treated. Approximately 80 per cent of internal mammary node metastases are located in the first three levels. It is our belief that if metastases are in the inconstant lower nodes or have crossed the midline the possibility that further spread has already occurred is too great to warrant radical therapy. Moreover, since we attempt to deliver a minimum of 5000 r tumor dose in four weeks to the parasternal area,

the skin dose is about 7000 r and morbidity would be excessive if a larger area of skin were treated to this dose level. A daily tumor dose of 200 rads is given to a total of 5000 rads for the parasternal field, and a daily tumor dose of 225 rads is given to the supraclavicular field to a total of 5500 rads, in five weeks Only a mild skin reaction is noted in the supraclavicular field The parasternal field develops a brisk epidermitis with desquamation of the skin, but subsequent healing occurs in six to eight weeks The resultant skin atrophy and telangiectasia are moderate if careful attention is given to skin care after treatment The chest wall is not routinely treated.

Primary Irradiation Therapy

The patients generally submitted to this method of treatment are those that are locally inoperable (*see* Treatment of Inoperable Cancer p 115) Lenz[18] reported on 46 patients treated by radiation therapy alone Doses of 5500 to 8000 r were administered to the breast and axilla over a period of two to three months At the end of five years only 10 patients were alive and symptom free Watson[37] reported on all cases of breast carcinoma treated at the Cancer Clinics in Saskatchewan He divided his cases into three broad groups group 1 includes cases without known secondary nodes group 2 includes those with secondary axillary nodes and group 3 includes all other cases Of the group 1 cases treated from 1932 to 1943 only 57 were given radiation alone and 52.6 per cent of these survived five years In group 2 cases there were 77 cases treated by radiation alone in the same time period and 22 1 per cent of these survived for five years In subsequent years "operable" cases were rarely submitted to radiation therapy alone, and adequate data are not available Baclesse[4] treated 130 cases with irradiation alone but no Stage I cases were included in this series The dosage ranged from 4000 to 9000 r given over a protracted period, and the maximum skin reaction was a dry desquamation Forty-one cases (31.2 per cent) survived for a minimum of five years with the highest survival rate in cases receiving over 6000 r

A major problem encountered with primary irradiation therapy is the marked skin reaction that occurs if tumor doses of 4000 to 5000 r are given in five to six weeks with 200 kilovolt *x* rays Baclesse[4] avoids this with exceptionally protracted therapy but most radiotherapists believe the optimum time-dose relationship involves a tumor dose of 5000 r in five to six weeks The skin of the axilla is particularly sensitive to high doses of irradiation, possibly because of contact with other skin surfaces and maceration. The management of large areas of desquamation can be very difficult. In some cases therapy must be discontinued before the desired tumor dose is given because of the severity of the skin reaction

The absence of severe skin reaction with supervoltage permits the delivery of a tumor dose of 5000 to 5500 r in five to six weeks. The patients also have less

systemic reaction to the irradiation and, therefore, tolerate the higher dosage. Supervoltage x-rays cannot be used in the treatment of the internal mammary chain of nodes because of the high depth dose and injury to the underlying lung and mediastinal structures Therefore, a compromise method must be used Such a method utilizes supervoltage irradiation for the breast, chest wall, axilla and supraclavicular areas, and lower voltage x-rays for the upper parasternal area (Fig 14)

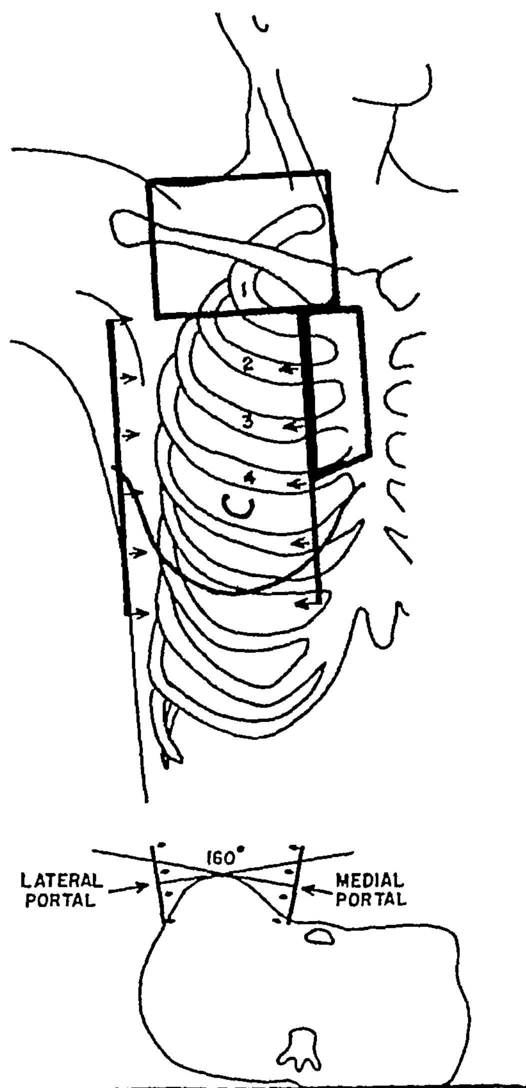


Fig 14 —Portals used for primary irradiation of breast carcinoma Supravoltage x-rays are used for breast, axillary and supraclavicular areas 140 kilovolt x-rays are used for parasternal area

The isodose pattern that supervoltage irradiation develops for the treatment of the chest wall is seen in Figure 15 Hare[16] has developed a rotational scanning method using 2 mev x-rays

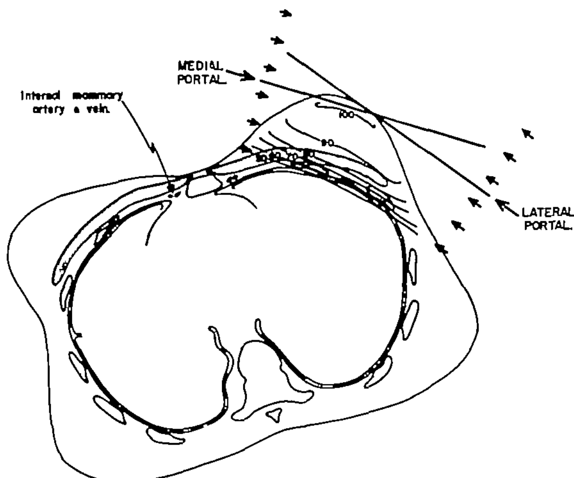


Fig. 15 —Isodose pattern obtained with supervoltage x rays in the treatment of breast carcinoma

Simple Mastectomy Plus X Ray Therapy

The employment of intensive x ray therapy after simple mastectomy has been espoused primarily by McWhirter[23] He has treated the largest series of patients by this technique, and reports a crude five year survival rate of 42 per cent in 1882 cases A simple mastectomy is done to remove the primary tumor confirm the diagnosis histologically and reduce the mass of tissue that must be irradiated After healing of the wound intensive fractionated x ray therapy is given, utilizing an x ray beam with a minimum half value layer of 3 7 mm Cu To avoid a severe reaction of the underlying pulmonary parenchyma tangential fields are employed. The medial tangential field border is placed 2 cm lateral to the midline on the uninvolved side in an attempt to irradiate the internal mammary chain on the involved side The axillary and supraclavicular chain of nodes is irradiated via two opposing fields, and a minimum tumor dose of 3750 r in three weeks is considered a radical treatment with a maximum dose at any point of 4250 r

The main point in McWhirter's[22] method of treatment is that simple mastectomy and x-ray therapy, given in his prescribed fashion, can be administered to 85 per cent of all cases of cancer of the breast, and thus offers a chance of cure to more patients. McWhirter[22] claims that at a maximum, only 14 per cent of all cases treated can be placed in a "disputable group" in which radical mastectomy alone might be equally or more effective than simple mastectomy and radiotherapy. To facilitate the presentation of his data, McWhirter has divided his cases into three groups as follows:

1. Operable (Manchester Stage I and II)
2. Locally advanced (Manchester Stage III and approximately half of Stage IV)
3. Distant metastases (the remainder of Manchester Stage IV cases)

With this classification his results are summarized in Table 4.

Table 4.—Results of Simple Mastectomy and Radiotherapy in the Treatment of Breast Cancer (McWhirter, Courtesy of Brit. J. Radiol., 1955).

All Cases of Primary Breast Cancer Recorded

	1941–47 Five-year Crude Survival Rate			*1941–42 Ten-year Crude Survival Rate*		
Stage of Disease	*Total*	*No. Alive*	*% Alive*	*Total*	*No. Alive*	*% Alive*
Operable	1063	612	58	254	99	39
Locally advanced	546	162	30	157	23	15
Distant metastases present	273	12	4	69	0	0
Total	1882	786	42	480	122	25

When it is realized that this series represents all patients presenting themselves for treatment, and is essentially unselected, the results are, indeed, satisfactory. Ackerman[1] has evaluated this series and offers criticisms of the method. He emphasizes the failure on McWhirter's[22] part to present adequate histologic proof that x-ray therapy in the dosage employed destroys nodal metastases. In the few cases that did have follow-up biopsies of axillary nodes, active tumor growth was noted. It may be that these were tumors with particularly aggressive growth characteristics. However, though there is a spectrum of response to a given dosage, McWhirter[22] offers no proof beyond survival that the nodal metastases were sterilized. *If in fact they were not, and only encased in a fibrous scar,* then in time there will be a recrudescence and dissemination. This may account to some degree for McWhirter's less satisfactory ten-year crude survival rate of 25 per cent. It is McWhirter's clinical impression that metastatic disease in the axilla is better controlled by the treatment given than is the primary disease in the breast. This view concurs with that of Levitt,[20] who stated that enlarged nodes due to carcinoma of the breast are at least as radiosensitive as the primary

and the end results are more permanent than in the primary growth Such a claim may be true when expressed in relative fashion, but does not imply that all carcinoma of the breast metastatic to the axillary nodes is radiosensitive It may be that a cancer can be controlled without eradicating all of its cells, and that the alteration by irradiation of cancer cells, or the tissues in which they lie brings about a dormant state adequate to control the cancer

As the need arises McWhirter[22] also uses other tools available to aid the breast cancer patient, such as hormones or ovarian sterilization Although this may confuse the evaluation of his series this practice cannot be condemned, and actually is found in many surgical series[35] The morbidity experienced by the patients undergoing this form of treatment cannot be dismissed but is difficult to assess. Ackerman believed that the morbidity was high and noted 47 serious postirradiation sequelae, including fractured ribs and clavicle

In the final analysis McWhirter s[22] contribution has been significant in that he has shown that breast cancer can be treated satisfactorily by means other than radical mastectomy Conceivably McWhirter s good results may be attributable to the avoidance of radical mastectomy *per se* rather than to his program of radiation therapy The very early cases in which simple mastectomy was suffi cient were not over treated and the equivocally operable cases had treatment adequate to control and restrain the disease without dissemination as a result of injudicious radical surgery

Objections can be made to McWhirter s[22] method of treating breast carcinoma A tumor dose of 3750 r in three weeks may be as efficient as a larger dosage over a more protracted period of time, but most investigators have found 3750 r inadequate for the eradication of breast carcinoma in the majority of patients It is our belief that 5000 r in five weeks is the *minimum* tumor dose necessary to control effectively breast carcinoma McWhirter also does not present any isodose patterns to substantiate his contention that the internal mammary chain of nodes is effectively treated by his tangential fields

The most serious error in McWhirter s work is that he has rigidly applied a single treatment method to a disease as variable as breast carcinoma Since he failed to do a carefully controlled clinical trial, valid conclusions as to the merit of this form of treatment cannot be drawn

Inoperable Cancer of the Breast

The primary method of treatment of patients with this situation is by irradiation, but hormone therapy and simple mastectomy are added when indicated There are two broad groups those that are inoperable because of regional spread, and those that are inoperable because of distant spread

A. *Regionally inoperable* A vigorous course of x ray therapy as described previously (p 111) is warranted in these cases A simple mastectomy can be done when the breast or primary tumor is of massive proportions and

radiation difficult. Otherwise, surgery should be withheld. Castration (surgical or *x*-ray) is performed on all patients having estrogenic activity as determined by vaginal smear examination. Further hormonal measures are withheld until distant metastases require their use.

B. Inoperable by virtue of distant metastases. Roentgen therapy to the primary breast tumor is administered if ulceration is present or seems imminent. Other areas are treated by irradiation as the clinical situation dictates, and only to palliation dose levels. Simple mastectomy is rarely necessary. Hormone treatment, such as, castration, the administration of androgens or estrogens, adrenalectomy or hypophysectomy are utilized as indicated.

Unusual Malignant Tumors of the Breast

Non-epithelial tumors of the breast that exhibit malignant characteristics are rarely seen by the radiotherapist. Many of these tumors are exceptionally radioresistant and radiotherapy is unwarranted. In this group of radioresistant tumors are fibrosarcomas, liposarcomas, and malignant cystosarcoma phyllodes. Surgery offers the only hope of cure in these patients.

Hodgkin's disease has been reported to originate in the breast, but more often appears as a manifestation of generalized disease. Similarly, lymphosarcomas and leukemia have been discovered in the breast. The majority of these lesions respond to radiotherapy, although the patient eventually succumbs to spread of the disease. If it can be shown that the tumor is limited to one breast radical mastectomy is the preferred method of treatment. An alternative method is simple mastectomy and vigorous radiotherapy to the chest wall and lymph node drainage areas. A tumor dose of 3000 r in three weeks to the involved areas is advised using 200 to 250 kilovolt *x*-rays.

PALLIATION OF BREAST CANCER BY IRRADIATION

The palliative use of irradiation is undoubtedly its greatest contribution in the management of patients with advanced breast cancer. Nevertheless, each patient must be carefully examined roentgenographically and physically, before treating, to establish the extent of the disease and the rapidity of its development. To embark upon a vigorous course of palliative roentgen therapy without this knowledge may result in serious depletion of the patient's reserves. Each case is individualized. If the problem is one of local recurrence, and there is no evidence of spread, then a vigorous course of therapy is indicated. As an example, if the only manifestation of recurrence is a mass of supraclavicular nodes in a patient who is otherwise in good health, a long period of survival occasionally may be obtained by initiating a course of *x*-ray therapy to the supraclavicular fossa and internal mammary chain of nodes. A tumor dose of 4000 to 5000 r is given within a five-week period. The physical factors employed for the supra-

clavicular field are 200 to 250 kilovolts peak with a filter giving a half value layer of 1 mm of Cu and a target skin distance of 50 cm. If supervoltage therapy is available its use in the supraclavicular area is indicated because of ease of administration and relative comfort to the patient.

Roentgen therapy offers a convenient and efficient method of dealing with skin recurrences or skin metastases They are most frequently found on the chest wall but can be found in other areas. Physical factors utilized vary slightly depending on the thickness of the tumor but usually 100 to 140 kilovolts peak, with a filter giving a half value layer of from 4 mm Al to 0.5 mm Cu, and a target skin distance of from 25 to 50 cm., will suffice A field size adequate to cover the lesion with a moderate margin is used, and a tumor dose of 3500 to 4000 r is given in three and one half to four weeks If the field size is small (less than 50 sq cm) treatment can be given 3 times weekly at a rate of 400 r tumor dose per treatment. If the area encompassed is larger daily treatments of 200 to 250 r tumor dose are advised to allow the normal tissues to recover Tangential fields are unnecessary for the treatment of small recurrences on the chest wall with the lower kilovoltages since the attenuation of the *x* ray beam is sufficient to prevent serious injury to the lung parenchyma. If the field is over 50 sq cm tangential fields are useful in preventing radiation pneumonitis

Soft tissue metastases in sites other than the skin occur frequently in breast cancer and *x* ray therapy for them is warranted if symptoms arise Unilateral pulmonary parenchymal metastases can be arrested temporarily often enough to encourage their treatment. If supervoltage therapy is available parallel opposing portals accurately localized are used Only a small margin of normal tissue is irradiated in order to prevent extensive pulmonary fibrosis A tumor dosage of 4500 to 5000 r in four to five weeks is given With 200 to 250 kilovolt *x* rays it is difficult to give dosages in this range without bringing on a moist desquamation of the skin Therefore multiple fields are employed to deliver tumor doses of 3500 to 4000 r in four weeks This will cause a moderate radiation pneumonitis and meticulous care of the patient is necessary to prevent serious complications.

Bilateral, pulmonary parenchymal, hilar or pleural metastases are rarely relieved with external *x* ray therapy Pleural metastases with a rapidly accumulating effusion is helped by the instillation of radioactive colloidal gold or chemotherapeutic agents, such as nitrogen mustard or Thio-TEPA (*see* chapter on Chemotherapy p 125) Similarly visceral metastases do not respond well to roentgen therapy Ascites occasionally is helped by the instillation of radioactive colloidal gold or chemotherapeutic agents Intestinal obstruction due to metastases must be corrected surgically

Brain or spinal cord metastases that can be accurately localized, preferably both clinically and roentgenographically are treated with *x* ray with temporary benefit. They receive a tumor dose of 3000 to 3500 r in four to five weeks Physical factors are 200 to 250 kilovolts peak, half value layer 1 to 2 mm Cu and a target skin distance of 50 cm The region involved is best irradiated through

opposing or oblique fields to avoid the moist skin reaction that occurs if only one field is used

Bone metatases occur in over half the patients with breast carcinoma, and the majority of these metastases cause symptoms. It is in the relief of pain from these metastases that x-ray therapy is most often employed The vertebral column, pelvis, thoracic cage, skull and upper femora are commonly involved Considerable destruction of normal bone is necsssary before such metastases are detected roentgenographically The lesions are usually osteolytic, but can be osteoblastic or mixed Patients with obvious metastatic disease elsewhere, who have pain in a specific region but show negative roentgenograms, probably have metastatic involvement and treatment is given empirically

Treatment of bone metastasis not only relieves pain, but will often prevent fractures or neurologic complications If multiple areas are involved care must be exercised to prevent undesirable radiation side effects due to the large volume of tissue being irradiated

Physical factors of the x-ray beam generally used for the treatment of bone metastases are 200 to 250 kilovolts peak, half value layer of 1 to 2 mm Cu and a target-skin distance of 50 cm Portal size will vary with the situation encountered, but a severe skin reaction is to be avoided, and multiple oblique or opposing fields are necessary A daily tumor dose of 200 to 250 r is given to a total tumor dose of 2000 to 2500 r in two to three weeks This will bring relief of pain in about 60 to 75 per cent of patients and frequently many comfortable years of survival Re-ossification and recalcification of the involved area will often be demonstrable roentgenographically With a return of symptoms, the area may be safely re-treated if the initial dosage was not above 3000 r The limiting factor is usually the skin reaction, but careful administration of the x-ray therapy and meticulous care of the skin will allow re-treatment in most instances A tumor dosage of 2000 to 2500 r is desirable, but the treatment time can be extended if necessary to avoid moist desquamation

Castration in women at the menopause or premenopausally has been used for many years as a means of altering hormonal activity and thus upsetting the tumor's dependence on estrogens The time to employ this tactic in the course of the disease has been a source of controversy and still is undecided This has been discussed in a previous chapter and a method of approach outlined (*see* p. 80)

The finding that x-ray castration is not permanent has caused many to turn to surgical castration Mere cessation of menses is not sufficient to insure suppression of ovarian estrogenic activity Patients undergoing roentgen castration should be checked for the development of typical castration patterns in their vaginal smears before the administered dose of x-rays is considered adequate

It has been our policy to eradicate ovarian function with x-ray therapy by utilizing a graded dosage, depending upon estimated ovarian activity Patients who are in the menopause or up to five years postmenopausal receive an ovarian

dosage of 1500 to 1800 r in two and one-half weeks Patients who are approximately five years premenopausal receive an ovarian dosage of 1800 to 2000 r in two and one-half weeks while those more than five years premenopausal (utilizing age forty seven as the average age of onset of menopause) will be given 2200 to 2500 r in three weeks. The physical factors are 200 to 250 kilovolts peak, half value layer 1 to 3 mm of Cu, and 50 to 70 cm target skin distance The field size usually measures 10 × 15 cm Opposing anterior and posterior portals are used giving between 150 to 200 r tumor dose per day (see Fig 16)

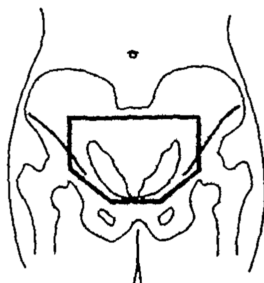


FIG. 16 —Anterior portal used in x ray castration A parallel and opposing posterior portal is also used

Side effects of irradiation, such as nausea, anorexia, cramping lower abdominal pain, and diarrhea are infrequently encountered, and tend to be minimal and transient The skin develops a moderate erythema which sometimes proceeds to a dry desquamation, and finally to minimal tanning A fall in the total white blood count, particularly of the lymphocytes will occur but this is not marked. Menopausal symptoms are noted in six to eight weeks in the premenopausal patients, and can be managed with sedatives as required Obviously estrogens should not be given to relieve the menopausal symptoms

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Chapter 10

TREATMENT OF METASTATIC BREAST CANCER BY OOPHORECTOMY, HORMONES AND CHEMOTHERAPY

ALTHOUGH important advances have been made in the techniques of operative surgery and radiation therapy many women with mammary cancer ultimately develop disseminated metastatic disease The clinical course of mammary cancer, being extremely variable, permits a large proportion of women to survive for more than five years[9] In the disseminated stage therapeutic emphasis shifts from an aggressive effort, directed toward cure, to a conservative and supportive approach where the goal of therapy is the relief of symptoms and distressing complications, and the prolongation of useful life Much can be done by the physician to assist individual patients from a medical and psychological standpoint

Helpful palliative therapy of metastatic breast cancer is achieved by hormonal manipulation, and in certain instances, chemotherapy These methods are not curative and the results obtained are usually of limited duration and extent They produce only a moderate degree of objective tumor regression, but considerable subjective improvement is experienced by the patient In many instances hormonal agents produce serious and undesirable effects Their application, therefore, requires careful individualization and control[5]

The rationale of hormone therapy of breast cancer rests on the concept that some breast cancers retain the characteristics of normal breast tissue, particularly with respect to hormone control It has been empirically established that the progress of mammary carcinoma may often be favorably, although temporarily, affected by the administration of large doses of sex hormones or by the removal of the sources of endogenous hormone production by oophorectomy, adrenalectomy or hypophysectomy The response to hormone therapy is dependent upon the age and menopausal status of the patient, and the extent and nature of the metastatic involvement Treatment with hormones is indicated only in patients with disseminated metastatic disease

Oophorectomy

In the premenopausal and early menopausal patient with disseminated breast cancer, where it has not been possible to control local or metastatic lesions by surgical and radiological means, the initial form of hormonal therapy to be employed is castration, preferably by surgery Oophorectomy produces objective

tumor regression in approximately 20 per cent of patients[4] Evidence of tumor regression associated with this procedure usually occurs within six weeks, and its suppressive effect may last for six months to several years Castration by radiation may be as effective as by surgery but the results produced by surgery are more prompt and more certain Oophorectomy in postmenopausal patients is followed by little clinical response but is to be considered. Prophylactic castration at the time of the initial radical mastectomy or before the development of symptoms from metastatic disease has not been demonstrated to increase the cure rate or to prevent or delay conclusively the onset of metastases (*see* p 80) Its early use deprives the patient of an important method of palliation at a later date[10] In the rarely seen male patient with carcinoma of the breast and disseminated metastases, orchiectomy offers a similar measure of temporary palliation[11]

Androgenic Hormones

Androgenic hormones were introduced in the treatment of advanced breast cancer with the belief that estrogens are in some way implicated in the etiology or activation of breast cancer and thus androgens might be expected to suppress breast cancer This does occur but the mechanism of action of androgens in producing suppression of mammary cancer is not understood.

The androgens are used as palliative agents at any stage of disseminated cancer and before or after the menopause They are employed in premenopausal patients with progressive metastatic disease following relapse or failure to respond to oophorectomy Subjective improvement, characterized by euphoria and relief of pain, occurs in 20 to 25 per cent of patients[4 7 8] Approximately two-thirds of patients with bone metastases experience relief from pain within one or two weeks after beginning therapy Soft tissue metastases are less responsive to androgens and regression occurs slowly Metastases in the liver and brain rarely respond.

The duration of androgen induced remissions is usually not over six to eight months, and seldom more than a year Treatment with androgen must be continued for ten to twelve weeks before its effect can be appraised. Occasionally a transient "flare" or exacerbation of symptoms produced by the tumor may precede the onset of a regression. Following response to therapy the androgen is continued until a relapse occurs Often further tumor regression will follow discontinuation of therapy so that it is desirable to wait several weeks before employing other methods of therapy When relapse occurs in the premenopausal patient after an adequate trial with androgen, adrenal steroids or surgical measures, such as adrenalectomy or hypophysectomy may be considered

Androgen preparations and their dosage

1. Testosterone propionate in oil, 100 mgm intramuscularly 3 times a week.
2. Methyltestosterone 25 to 100 mgm orally daily or 40 mgm sublingually daily

3 Fluoxymesterone, 20 mgm orally, daily

The last named is a new, potent androgen similar in effect to testosterone and having the advantage of oral administration [6] Long acting androgenic preparations are not recommended since their effect persists for two weeks and they cannot be readily discontinued if complications develop The clinical response with the androgens, though variable, has been better when given intramuscularly rather than by the oral route

Unpleasant and distressing side effects of androgen therapy include virilism, hirsutism, deepening of the voice, acne, flushing, sodium retention, and increased libido Hypercalcemia, which occurs in approximately 10 per cent of patients with extensive osteolytic metastases, is significantly increased with androgen treatment [1] Symptoms, which occur after several weeks or months of treatment, include drowsiness, unusual behavior, nausea and vomiting, constipation, polyuria, and ultimately coma and death

It is necessary to evaluate the level of urinary or serum calcium at regular intervals during androgen therapy Hypercalcemia, which is accompanied by an increased urinary calcium excretion, is readily detected with the urinary Sulkowitch test A 3 or 4 plus reaction is indicative of increased calcium excretion and is confirmed by a serum calcium determination

When patients develop evidence of hypercalcemia, prompt corrective measures are instituted These include withdrawal of the androgen, institution of a high fluid intake, ambulation when possible, removal from the diet of calcium-rich foods, such as, milk and cheese, and the administration of large doses of adrenal steroids Cortisone acetate in initial doses of 300 to 400 mgm per day, or prednisone in doses of 60 to 100 mgm per day often produce dramatic clinical improvement and a decrease in serum calcium levels In these patients, resumption of androgen therapy is undertaken with caution

Estrogenic Hormones

Estrogens are employed in patients five years beyond the menopause They are also used in males with widespread breast cancer. Tumor regression with this form of therapy is surprising in view of the stimulating effect of estrogen on the tumors of premenopausal patients The palliative value of estrogens has been established by empirical use [4,7,8] Large doses favorably produce objective regressions in soft tissue metastases and pulmonary metastases Ulcerated primary lesions may heal Estrogens are less effective on osseous metastases and patients with liver metastases seldom respond Subjective improvement is experienced by approximately half of the patients treated

The effect of estrogen therapy is usually evident within one to three months It should be administered for at least three months before concluding that the treatment is without value If the patient responds to therapy, estrogen is

continued until evidence of relapse occurs In the event of relapse the patient may be started on a trial of androgen therapy as described for the premenopausal patient Objective regressions produced by estrogens persist for six to eight months, occasionally longer Elderly patients have better response to estrogens than do younger postmenopausal patients Estrogen therapy should be started with caution in the latter group as treatment may occasionally produce an exacerbation of the cancer

Estrogen preparations and their dosage

1 Ethinyl estradiol, 3 mgm orally daily
2. Diethylstilbesterol, 15 to 30 mgm orally daily

Complications of estrogen therapy include sodium retention and edema, anorexia, nausea, vomiting, uterine bleeding, pigmentation of the nipples, and occasionally exacerbation of tumor growth. In most instances nausea and vomiting are controlled by chlorpromazine administration in oral doses of 10 to 25 mgm., 3 times daily In elderly patients with heart disease sodium retention may precipitate congestive heart failure Appropriate dietary sodium restriction and diuretics are employed, and careful supervision is maintained Uterine bleeding may be controlled by sharply increasing the dose of estrogen.

Adrenal Steroid Hormones

Administration of adrenal steroid hormones, cortisone prednisone, and prednisolone, produces marked subjective improvement in the form of euphoria, improvement of appetite, increased vigor and other manifestations. Unfortunately they do not produce a significant degree of tumor regression and are best reserved for palliation of patients with far advanced disease who have received all above described methods of treatment. Dramatic relief of symptoms produced by cerebral metastases and by hypercalcemia may follow the administration of adrenal steroids They are also of occasional value in the treatment of hemolytic anemia accompanying breast cancer Complications of therapy with adrenal steroids include Cushing's syndrome, edema due to sodium retention, hypertension, diabetes peptic ulcer and psychosis

Adrenal steroid preparations and their dosage

1 Cortisone acetate 100 to 200 mgm orally daily
2. Prednisone, 40 to 100 mgm orally daily
3. Prednisolone 40 to 100 mgm orally daily

Chemotherapy

Systemic chemotherapy with currently available compounds is of little practical value in the majority of patients with far advanced breast cancer Temporary subjective improvement, and infrequent tumor regression have been ob-

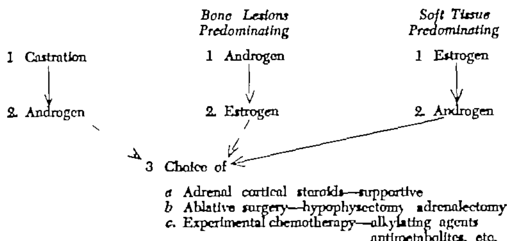
served occasionally following the intravenous administration of nitrogen mustard. Reports of benefit from the phosphoramide group of drugs have not been confirmed.[2,12] At present, the most useful application of chemotherapy in the management of breast cancer is in the control of recurrent malignant pleural effusions and ascites. The direct injection of nitrogen mustard into the involved cavity will eliminate or suppress an effusion in approximately two-thirds of the patients.[13] This method of control compares favorably with results obtained using radioactive gold or chromium phosphate. It has the important advantage of being easily administered, readily available, inexpensive, and without radiation hazard.

The procedure is carried out as follows. Approximately half of the pleural or ascitic fluid is withdrawn and nitrogen mustard is injected into the cavity. The dose employed is 0.4 mgm./kg. of body weight, amounting to a total dose of 20 to 30 mgm. in the usual patient. The solution is prepared immediately before administration, so as to avoid loss of potency through hydrolysis, and is dissolved in 50 cc. of normal saline. In patients with pleural effusions the drug is injected through the same needle used for thoracentesis, whereas in patients with ascites it is injected at a different site in the peritoneal cavity by means of a long, #22 gauge needle. Care is taken so that a free flow of fluid is obtained from the cavity before the drug is injected, assuring that it is not injected into the tissues. Following injection of nitrogen mustard the patient is placed in a variety of positions in order to distribute it throughout the pleural or abdominal cavity. On the following day the remaining fluid is withdrawn from the body cavity.

Pain is seldom experienced following injection of nitrogen mustard into the pleural cavity, but pain, nausea, vomiting, and peritoneal irritation may be experienced for several days following its injection into the peritoneal cavity. Nausea and vomiting usually are experienced within a few hours following administration of nitrogen mustard, but can be controlled with 25 mgm. of chlorpromazine, intramuscularly, given immediately before the procedure and at two hour intervals for 2 or 3 doses following the injection. Bone marrow depression is mild with this method of administration, and repeated courses of nitrogen mustard are given at two or three week intervals if necessary. The hematologic status is watched carefully nonetheless. Extra caution should be employed in patients who have received extensive radiation therapy to bone metastases.

A suggested plan of therapy for disseminated mammary carcinoma is shown in Table 5. It is anticipated that many new and more effective synthetic androgen and estrogen derivatives will be made available in the near future. In addition, a clarification of the value of presently available hormones will result from the cooperative research effort being conducted by the National Cancer Chemotherapy Service Center of the National Cancer Institute, and a large group of cooperating medical schools.[7]

Table 5



At any time during course of disease
1 Radiation therapy for localized lesions.
2 Nitrogen mustard, or radioactive materials for intracavitary
injection for malignant effusions and ascites

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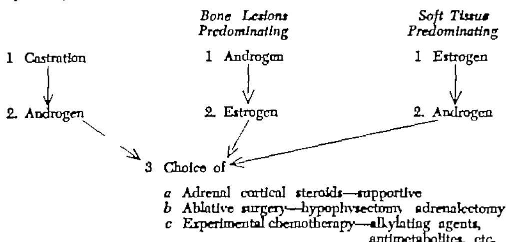
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Table 5



a Adrenal cortical steroids—supportive
b Ablative surgery—hypophysectomy adrenalectomy
c Experimental chemotherapy—alkylating agents, antimetabolites, etc.

At any time during course of disease
1 Radiation therapy for localized lesions.
2 Nitrogen mustard, or radioactive materials for intracavitary injection for malignant effusions and ascites.

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served occasionally following the intravenous administration of nitrogen mustard Reports of benefit from the phosphoramide group of drugs have not been confirmed[2,12] At present, the most useful application of chemotherapy in the management of breast cancer is in the control of recurrent malignant pleural effusions and ascites The direct injection of nitrogen mustard into the involved cavity will eliminate or suppress an effusion in approximately two-thirds of the patients[13] This method of control compares favorably with results obtained using radioactive gold or chromium phosphate It has the important advantage of being easily administered, readily available, inexpensive, and without radiation hazard

The procedure is carried out as follows Approximately half of the pleural or ascitic fluid is withdrawn and nitrogen mustard is injected into the cavity The dose employed is 0 4 mgm kg of body weight, amounting to a total dose of 20 to 30 mgm in the usual patient The solution is prepared immediately before administration, so as to avoid loss of potency through hydrolysis, and is dissolved in 50 cc of normal saline In patients with pleural effusions the drug is injected through the same needle used for thoracentesis, whereas in patients with ascites it is injected at a different site in the peritoneal cavity by means of a long, #22 gauge needle Care is taken so that a free flow of fluid is obtained from the cavity before the drug is injected, assuring that it is not injected into the tissues Following injection of nitrogen mustard the patient is placed in a variety of positions in order to distribute it throughout the pleural or abdominal cavity On the following day the remaining fluid is withdrawn from the body cavity

Pain is seldom experienced following injection of nitrogen mustard into the pleural cavity, but pain, nausea, vomiting, and peritoneal irritation may be experienced for several days following its injection into the peritoneal cavity Nausea and vomiting usually are experienced within a few hours following administration of nitrogen mustard, but can be controlled with 25 mgm of chlorpromazine, intramuscularly, given immediately before the procedure and at two hour intervals for 2 or 3 doses following the injection Bone marrow depression is mild with this method of administration, and repeated courses of nitrogen mustard are given at two or three week intervals if necessary The hematologic status is watched carefully nonetheless Extra caution should be employed in patients who have received extensive radiation therapy to bone metastases

A suggested plan of therapy for disseminated mammary carcinoma is shown in Table 5 It is anticipated that many new and more effective synthetic androgen and estrogen derivatives will be made available in the near future In addition, a clarification of the value of presently available hormones will result from the cooperative research effort being conducted by the National Cancer Chemotherapy Service Center of the National Cancer Institute, and a large group of cooperating medical schools[1]

Table 5

Premenopausal or Early Menopausal	*Postmenopausal*	
	Bone Lesions Predominating	*Soft Tissue Predominating*
1 Castration	1 Androgen	1 Estrogen
↓	↓	↓
2. Androgen	2. Estrogen	2. Androgen

↘ 3. Choice of ↙

a Adrenal cortical steroids—supportive
b Ablative surgery—hypophysectomy adrenalectomy
c Experimental chemotherapy—alkylating agents, antimetabolites, etc.

At any time during course of disease
1 Radiation therapy for localized lesions.
2. Nitrogen mustard, or radioactive materials for intracavitary injection for malignant effusions and ascites

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pter 11

'RENALECTOMY AND METASTATIC EAST CANCER

E first successful total adrenalectomy in man was performed by Huggins and ' in 1945 on a patient suffering from carcinoma of the prostate Adrenal iciency developed since cortisone and similarily active compounds were ailable at that time With the advent of cortisone Huggins again attempted ialectomy for the treatment of metastatic carcinoma In 1952 he published al papers on adrenalectomy describing its effect on patients with metastatic noma of the breast [8 9]

e procedure advocated by Huggins consists of oophorectomy if not already rmed, and total adrenalectomy The chief contraindication to adrenalec is extensive liver metastasis and probably cerebral, as well. Although s are variable, approximately one-third of the patients show some palliative it. In all of the series of any numerical size it is evident that the majority tients are unresponsive When effective there is decrease in pain from bony tases, regression of soft part recurrences, absorption of pleural and ascitic and a very definite overall improvement in well being The duration of it varies, as a rule nine to twelve months, but periods up to twenty four hirty months are reported [1 2,3,11 12] The result may be dramatic and this is kept in mind despite the numerous failures

cause of these occasionally dramatic results the criteria for selecting patients prime importance Unfortunately no such reliable criteria have yet been coming In his initial reports, Huggins[7 8 9] impression that the histologic rn of differentiation of the tumor may predict its sensitivity to adrenalectomy ot been found acceptable Age is also an unpredictable factor and has n variations young, premenopausal women may do well, and older women no beneficial response whatsoever although the reverse of this would be ted Pearson[11 12] designed a test for the selection of patients based on m excretion studies of the urine Exceptions to this occur and if only issue metastases are present this determination is not applicable

difications of oophorectomy and total adrenalectomy have been reported.[1 4 5] e series,[1] in addition to oophorectomy and adrenalectomy the adrenal cortex re-implanted into the mesentery of the small intestine In this way it is ned that adrenal estrogens and androgens are metabolized by the liver e same manner as the gonadal steroids, by transplanting the adrenal cortex

into the portal circulation The liver would thus inactivate the so-called "carcinogens" without complete inactivation of essential cortical steroids. Twenty-two patients with adrenal cortex autotransplantation were studied[1] and it was demonstrated that the transplanted adrenal cortex was viable and functioned physiologically The therapeutic results obtained by this method closely parallel those reported by others with oophorectomy and adrenalectomy alone.[2,3,6,9,11] Its advantage lies in the smaller dosages of cortisone necessary to maintain the patient postoperatively, but all require some substitution therapy Galante[5] has reported on a few cases in which the adrenal vein was anastomosed to the splenic vein, with similar results Because medical (cortisone) therapy is relatively satisfactory adrenal grafting procedures are not commonly performed

The recent long term follow up report of Dao and Huggins[3] evaluates 52 consecutive patients with metastatic mammary cancer who underwent adrenalectomy They felt that "significant remissions occurred in 20 patients" and 2 survived more than five years A study of their statistics reveals that 37 patients were dead within one year, 43 within two years, 45 within three years, and 49 within four years Although the mean survival of their patients with generalized metastasis was 27 6 months *this must be evaluated in relation to the actual* number surviving

As with all traumatic therapeutic measures, particularly in evaluation of our present problem, *i e*, adrenalectomy for cancer of the breast, it is imperative to give careful consideration to the following

1 The quality of the therapy, extensive surgery
2 The relative number of patients that may be benefited
3 The quality and duration of the therapeutic result, noncurative

The surgery is extensive and need not be emphasized (*see* below) Comment has already been made regarding the number of patients benefited It is felt that the quality of the therapeutic result has been misleading in most reports, that palliation is more apparent than real, and not different or superior to that obtained by the more simple measures of oophorectomy and hormone manipulation (*see* p 122) One must bear in mind that the adrenalectomized patient, even with the best of steroidal substitution, is in no way a complete human being in good homeostasis The adrenal glands secrete numerous steroids, few of which are replaced, and these are modified synthetic products They are given at intervals which may bear little relationship to the physiological needs of the patient. Certainly such patients are able to function, but their resistance is low, not only to infection, but to the stress and strain of ordinary environmental influences[13]

On the other hand, adrenalectomy has reinforced our belief that certain mammary cancers demonstrate partial hormone dependency When the effect of oophorectomy and oral or parenteral hormones has subsided, it is a procedure worthy of consideration This may be especially so in patients who have responded well to previous hormone therapy To employ this procedure earlier

in the course of the disease does not seem warranted in view of the sometimes dramatic results of oophorectomy and hormone treatment alone

Perhaps the greatest contribution of adrenalectomy is that it has emphasized the inter relationship of certain cancers and the endocrine system The increased knowledge in physiology and chemistry derived from studies of the adrenalec tomized patient will prove valuable in reaching a physiologic solution to breast cancer

Pre- and Postoperative Management

In addition to a thorough physical examination, and frank discussion with the patient and her family of the operation and its results the following studies are obtained before adrenalectomy is performed

1 X rays of chest and skeleton
2 Electrocardiogram
3 Non protein nitrogen
4 Serum Sodium
5 Serum Potassium
6 Serum Chloride
7 Serum Calcium
8 Serum Phosphorus
9 Serum Protein
10 Packed cell volume
11 Complete blood count
12 Urine analysis

Experience has shown that no special preoperative medication is necessary[1] steroid administration is started when the patient is on the operating table A "cut-down" using a #13 or #15 gauge polyethylene tube is placed in an arm or leg vein and 1 liter of 5 per cent glucose in water containing 100 mgm of hydrocortisone, is administered by constant drip (Plate 42) During induction of anesthesia 250 cc are injected rapidly and thereafter blood pressure is kept at the patient's normal preoperative level by varying the number of drops per minute By the end of the operation 400 to 600 cc containing 40 to 60 mgm of hydrocortisone have been given Whole blood is added as needed either through the same tubing or through another "cut-down" During the first twenty four hours about 100 to 200 mgm of hydrocortisone is given Intravenous hydrocortisone solution is continued until the patient is able to take oral medica tion without nausea or vomiting, usually by the fourth or fifth day As an alternative cortisone in dosages of 100 to 150 mgm a day may be given intra muscularly should the intravenous route be troublesome Because of the short life of hydrocortisone about four hours, care is necessary lest the intravenous apparatus shut down and the patient be without medication By using cortisone intramuscularly this danger is avoided

In some patients who are very debilitated or aged 25 to 100 mgm of cortisone are given intramuscularly the night before surgery Five to 10 mgm of desoxy corticosterone (DOCA) sublingually and oral salt, 4 gm., can also be given the day before[6] This has not been necessary in the majority of patients[1]

The total daily postoperative fluid intake is kept at about 2500 cc, of which 1000 to 1500 cc is normal saline By the second day only 75 to 100 mgm of hydrocortisone are needed There is a gradual leveling off to between 50 and 75 mgm daily When oral hydrocortisone is given, 40 to 60 mgm a day are often sufficient, and at the time of discharge 20 to 40 mgm a day are satisfactory There are periods when the requirements increase due to a variety of clinical conditions [13]

On the third day an ampule containing KCl 1.8 gm, $MgCl_2$ 0.5 gm, and $CaCl_2$ 0 6 gm is given and continued daily to prevent hypokalemia Serum potassium and sodium levels are checked at frequent intervals

Sodium chloride in enteric coated tablets is given in doses of 1 gm 3 times daily after the tenth day In some patients a persistently low serum sodium level is restored to normal by an injection of 15 to 25 mgm of the long acting, repository form of DOCA, desoxycorticosterone trimethylacetate, once a month In others, 2 mgm, sublingually, daily, of regular DOCA as maintenance dosage is used

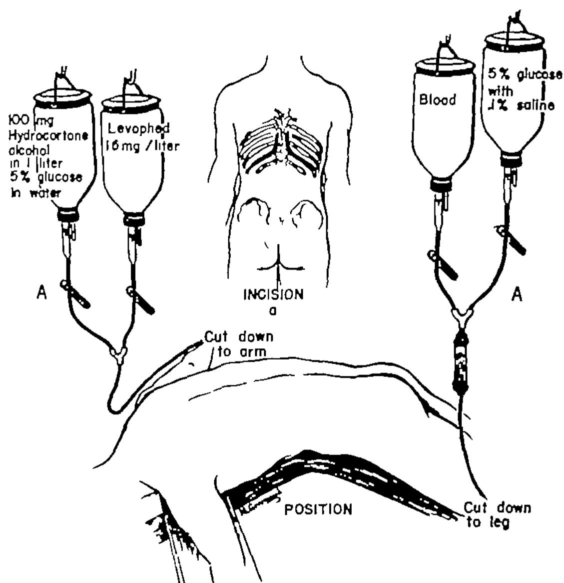
If shock occurs during the operation or afterwards it is combated with a 16 mg./Liter solution of L-Arterenol (levophed), 50 to 70 drops per minute, or regulated as needed to maintain normal blood pressure (Plate 42A) Renal shut down and paralytic ileus are other complications which are dealt with as they arise Close postoperative supervision, especially of the pulse and blood pressure, are essential, in addition to strict attention to fluid balance and electrolytes.

Surgical Technique of Adrenalectomy

Removal of the adrenal glands is combined with bilateral oophorectomy if the latter has not been previously performed The abdominal approach through a long upper transverse incision is strongly recommended by some[1] It enables one to remove the ovaries simultaneously and is essential if cortical transplant is to be done A posterior approach, through the back, is also adequate, and by using two teams of surgeons probably quicker The adrenal glands are, after all, subdiaphragmatic organs and more often than not situated high in the retroperitoneal space [10] They are more superficial when approached from behind than in front Nagamatsu[10] has described a dorsolumbar incision which facilitates removal If this method is used, the ovaries are removed first by laparotomy The patient is then turned, and adrenalectomy performed Lessened morbidity, diminished ileus, simultaneous exposure of each adrenal (if two teams operate), and shortened operating time are the advantages of this approach.

There is some disadvantage in turning the patient after laparotomy, and extra caution is necessary in turning the patient back again following adrenalectomy Change in position may caused marked depression of the blood pressure Aside from these two factors the method has proved useful and satisfactory Since

PLATE 42


100 mg
Hydrocortone
alcohol
in 1 liter
5% glucose
in water
Levophed
16 mg /liter
Blood
5% glucose
with
.1% saline
A
INCISION
a
A
Cut down
to arm
POSITION
Cut down
to leg

the abdominal route is more familiar, the posterior approach only is illustrated in accompanying diagrams

The patient is placed prone on the operating table with the kidney rest lying just below the costal margin Slight "jack-knife" position is used (Plate 42) Endotracheal anesthesia is essential Incisions are made in curved, hockey stick fashion, starting at the ninth dorsal spine and carried downward and laterally along the course of the 11th and twelfth ribs to the margin of the rectus muscle (Plate 42) Overlying musculature is incised and short segments of the eleventh and twelfth ribs are resected medial to their angles (Plate 43). The entire ribs are resected in the diagram, but this is not necessary. The costovertebral ligament is sectioned exposing the diaphragm The lateral arcuate ligament of the diaphragm (Plate 43) is divided below the pleural reflection, although in many instances the pleural cavity is entered The retroperitoneal space with kidney and adrenal glands is exposed (Plate 43) The adrenal glands are removed (Plates 44, 45, 46), usually with a little more difficulty on the right side due to the proximity of the vena cava The wound is sutured in layers (Plate 47) The pleural cavity, if entered, is closed under positive pressure with full lung expansion No drains are used (Plate 47) The patient is cautiously turned supine, and placed in bed.

PLATE 43

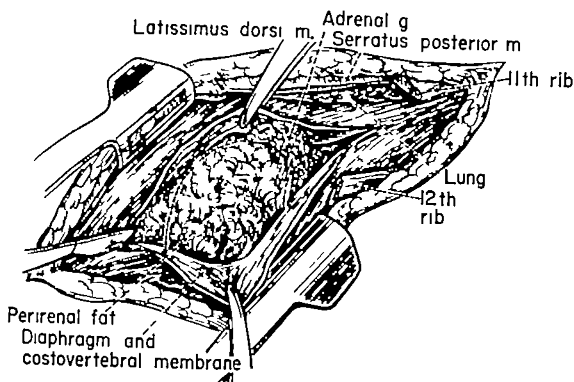


PLATE 44

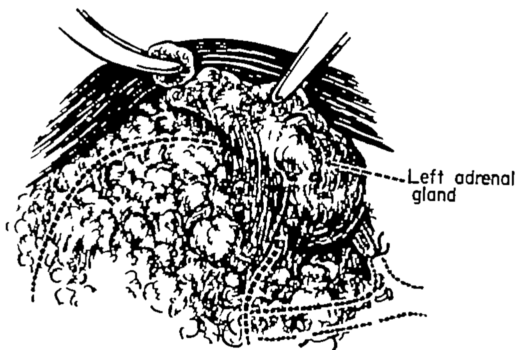


PLATE 45

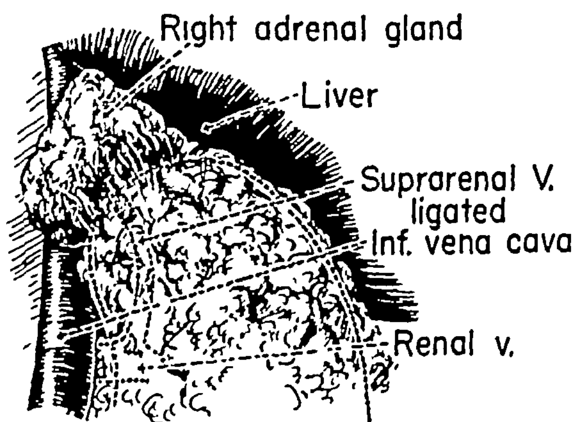


PLATE 46

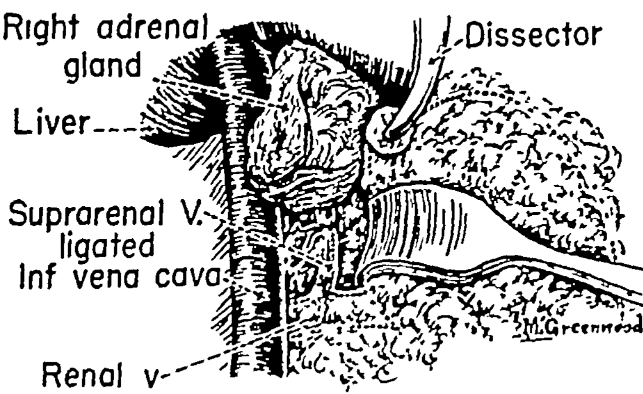
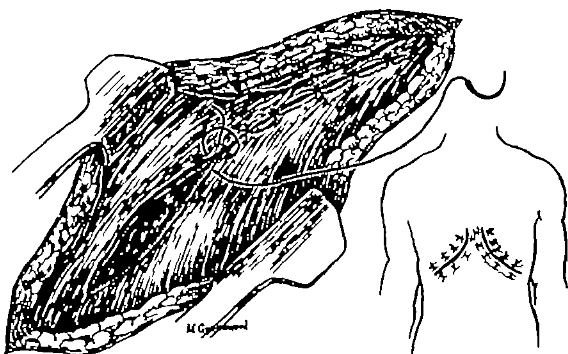


PLATE 47



Suturing diaphragm and costovertebral membrane

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Chapter 12

HYPOPHYSECTOMY AND METASTATIC BREAST CANCER

THE anterior pituitary gland produces several hormones which may influence the *growth of breast cancer These are follicle stimulating hormone and* interstitial cell stimulating hormone which control ovarian steroidogenesis lactogenic hormone which has a direct effect on breast tissue as well as maintenance of ovarian steroidogenesis adrenocorticotrophic hormone which controls adrenal steroidogenesis and somatotrophin, or growth hormone which may directly stimulate the growth of cancer tissue Thus hypophysectomy might be expected to modify the hormonal environment of metastatic breast cancer by eliminating these hormones

Many methods for the destruction of the human pituitary gland are currently being studied These include Surgical hypophysectomy by the trans-cranial, trans septal-sphenoidal, trans-ethmoid sphenoidal or the trans antral sphenoidal approaches irradiation hypophysectomy by proton bombardment with the syn chrocyclotron or by intrapituitary injection of radioactive substances such as radon seeds, yttrium 90 pellets or phosphorus 32 as colloidal chromic phosphate or pituitary stalk section which accomplishes a functional hypophysectomy by separating the anterior pituitary gland from the hypothalamic control centers There is no agreement regarding the superiority of methods which attempt actual removal over methods attempting destruction or neutralization As a matter of fact there is some question as to whether total removal is essential for effective therapy against mammary carcinoma [2,4,5,7,9,10]

That method which permits effective removal of function with the least danger and the fewest complications is the most desirable These criteria are satisfied with direct vision of the field including the important structures which are in anatomical relationship to the sella This consideration emphasizes a major advantage of the methods requiring craniotomy

Extirpation of a normal pituitary gland by transfrontal craniotomy allows the greatest control in protection of the hypothalamic and optic apparatuses, and maximum opportunity to prevent or control bleeding from the numerous arterial and venous structures in the immediate neighborhood Experience shows, how ever that complete removal has been very infrequent [5,8,1]

The trans septal sphenoid approach to the pituitary gland was developed by Oscar Hirsch[8] in 1910 It has been used extensively in the treatment of pituitary

tumors.[5,6] For a subtotal, functional hypophysectomy it is a logical approach, although by craniotomy or by a trans-antral-sphenoid technique, wider surgical exposure is obtained, and a more complete hypophysectomy accomplished. It is a non-shocking procedure, accompanied by little blood loss and performed under local anesthesia. If complete hypophysectomy is shown to give better palliation, more extensive procedures are warranted.

HORMONAL MANAGEMENT OF THE PATIENT UNDERGOING SURGICAL HYPOPHYSECTOMY

Preoperative determinations of the following afford a baseline for postoperative comparison: serum sodium, potassium, urea, protein bound iodine, and urine pituitary gonadotrophin titer.

The plan of hormonal management is as follows:

Cortisone acetate, 100 mgm., intramuscularly, the night before and the morning of surgery.

Hydrocortisone alcohol, 100 mgm., in 500 ml. 5 per cent glucose in water, intravenously, slowly during surgery.

Cortisone acetate, 50 mgm., intramuscularly, every six hours postoperatively. This dosage is slowly reduced and gradually shifted to oral cortisone so that by the fifth postoperative day the patient is on a daily oral maintenance dose of 25 to 50 mgm., of cortisone.

Fluids: 2500 ml. daily, including 5 to 10 grams of NaCl (86 to 172 mEq. Na daily).

Urine output is carefully measured, and if urine flow is consistently greater than 300 ml. per two-hour period, 3 units of pitressin tannate in oil is given intramuscularly and repeated every two or three days as indicated.

Vital signs are followed carefully during the immediate postoperative period. Should hypotension or shock develop, in addition to usual surgical management, 100 to 200 mgm. of hydrocortisone hemisuccinate is administered intravenously. This complication rarely occurs. Diabetes insipidus occurs more often following intracranial procedures in which the pituitary stalk is traumatized. It may be a transient or permanent development after hypophysectomy by any route and responds to pitressin tannate in oil, 3 units intramuscularly every two to three days.

Serum electrolytes are followed postoperatively to be certain that corticoid replacement is adequate. Thyroid extract is not routinely given because the development of hypothyroidism four to six weeks postoperatively may be a useful index to the completeness of hypophysectomy. Another index to the completeness of hypophysectomy is the disappearance of anterior pituitary gonadotrophin from the urine. It is advisable, therefore, to determine the serum protein bound iodine and the urine gonadotrophin titer at monthly intervals after hypophysectomy.

Totally hypophysectomized patients are usually well maintained on 25 to 50 mgm of cortisone (or 20 to 40 mgm of hydrocortisone) orally in divided doses daily and l thyroxine 0.2 mgm in a single oral dose daily During periods of stress the dose of cortisone is increased If severe it is wise to revert to parenteral therapy with intramuscular cortisone acetate and intravenous hydrocortisone hemisuccinate administering a total of 300 to 400 mgm of steroid over a twenty four hour period

DISCUSSION

Hypophysectomy by whatever route performed is a palliative procedure of limited value It is the final method of treatment which one may employ for a patient with disseminated breast cancer It has not supplanted adrenalectomy though theoretically it could In a few instances adrenalectomized patients will show further regression of their metastases following hypophysectomy [8,9,10] Unfortunately by the time most patients stop responding to the effects of adrenal ectomy they are too near death to warrant further operative procedures In addition, results with oophorectomy and hormones, though far from satisfactory are yet good enough not to be superseded by hypophysectomy (or adrenalectomy) performed in an earlier stage of the patient s disease Whether performing hypophysectomy at an earlier stage in the course of progressive metastases would increase comfortable longevity is open to question and awaits further study By the relatively simple means of oophorectomy and hormone manipulation one appears to accomplish equal results It is only after the effect of hormones subsides that the operative procedures of adrenalectomy and ultimately hypophysectomy are considered

The reported results of surgical hypophysectomy in patients with metastatic cancer of the breast indicate that about 20 to 50 per cent will achieve some palliation of their disease [2,3,7,10] This is of short duration, three to six months It is associated with objective regression of metastatic lesions particularly in the lungs or skeleton Subjective improvement, especially relief of pain, may be marked Older patients and patients with liver or brain metastases are less likely to respond Patients who have had some prior response to castration or hormone therapy do better Experience with trans septal sphenoid hypophysectomy has not been dramatic yet this approach is simple, carries little morbidity and is worthy of trial if hypophysectomy is to be performed

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